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Effect of Age and Gender on the Pharmacokinetics of Oral and IV Omadacycline, A New Class of Aminomethylcyclines

S. Ken Tanaka, PhD; Evan Tzanis; Stephen Villano, MD

Paratek Pharmaceuticals, King of Prussia, Pennsylvania, USA

ABSTRACT

Background: Omadacycline is the first of a new class of antibiotics, the aminomethylcyclines, currently in phase 3 clinical development as a once daily oral and intravenous (IV) formulation for CABP and ABSSSI. Two phase 1 studies were undertaken to evaluate the effect of age and gender on the pharmacokinetic (PK) of omadacycline after oral and IV administration in healthy volunteers.

Methods: Both were double-blind and placebo-controlled studies of single oral doses of omadacycline in subjects randomized in a 3:1 ratio to omadacycline or placebo. Study 1 included 4 subject groups: A) young males; B) young females; C) elderly males; D) elderly females. After an 8-hour overnight fast, each group received placebo or omadacycline 200 mg. Study 2 included healthy young male and female subjects who received a single 200 mg oral or 100 mg IV dose of omadacycline or placebo. Blood samples were obtained pre-dose, and 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 18, 24, 48, 72 and 96 hours post-dose to determine PK parameters.

Results: In Study 1 (23 subjects), a high degree of consistency was observed for the PK characteristics of a single 200 mg oral dose. No significant difference in drug exposure was observed between fasting young and elderly subjects. Both young and elderly females exhibited greater mean AUC_{inf} values than corresponding young and elderly male subjects (14.6 mg*h/L vs. 9.4 mg*h/L for all female and all male subjects; ratio 0.64, 90% CI: 0.52, 0.80). For elderly vs. young subjects, the mean ratio was 1.13 (90% CI: 0.91, 1.41). In Study 2 (24 subjects), evaluation of PK profiles showed a high degree of consistency between males and females who received a 200 mg oral dose of omadacycline. The AUC_{inf} ratio of males to females was 1.02 (2-sided 90% CI 0.69, 1.50). The geometric mean half-life was 17.2 hours for the males and 11.4 hours for the females. The AUC_{inf} for IV omadacycline exhibited more variability in female (18.4%) than in male subjects (4.9%) but the 90% CI for mean AUC_{inf} ratio for males to females was within the specified range (ratio 0.77, 90% CI: 0.67, 0.89). Omadacycline oral and IV formulations were well tolerated with no unexpected safety or tolerability adverse events.

Conclusion: After a single oral administration of 200 mg of omadacycline, female subjects demonstrated higher mean AUC_{inf} compared to male subjects. However, the exposure in females did not differ significantly after a single IV dose. No effect of age on omadacycline absorption and PK profile was observed. Thus, no dosage adjustment on the basis of patient age or gender is necessary.

INTRODUCTION

Omadacycline is a first in class aminomethylcycline antibiotic that is being developed as a once daily oral and intravenous (IV) monotherapy for acute bacterial skin and skin structure infections (ABSSSI) and community acquired bacterial pneumonia (CABP). *In vitro*, omadacycline is active against Gram-positive and Gram-negative aerobes, anaerobes, and atypical pathogens (Macone et al, 2014). Previous studies in patients with skin and skin structure infections showed that omadacycline was comparable to linezolid for clinical cure (Noel et al, 2012; Noel et al, 2012a). Studies in healthy volunteers have reported a half-life of approximately 17 hours. After 300 mg oral and 100 mg IV doses, peak concentration (C_{max}) was approximately 0.6 mg/L and 1.8 mg/L, respectively, and an area under the concentration (AUC) time curve was approximately 10 mg*h/L after each of these doses (Sun et al, 2011). However, it is important to evaluate the effect of age and gender on the pharmacokinetic (PK) profile to determine if dosage adjustment is needed in these patient populations. We report the results from two phase 1 studies that evaluated the effect of age and gender on the PK profile of omadacycline after oral and IV administration.

METHODS

- Two double-blind and placebo-controlled studies were conducted in healthy subjects randomized in a 3:1 ratio to omadacycline or placebo.
- Design:
  - Study 1
    - 4 groups:
      - A) young males (18-45 years)
      - B) young females (18-45 years)
      - C) elderly males (65-80 years)
      - D) elderly females (65-80 years)
    - After an 8-hour overnight fast, each subject received a single 200 mg oral dose (4 x 50 mg capsules) of omadacycline; subjects continued to fast for 4 hours after dosing.
  - Study 2
    - Healthy young male and female subjects (18-45 years)
    - After a 6-hour overnight fast, each subject received a single 100 mg IV or 200 mg oral (2 x 100 mg capsules) dose of omadacycline; subjects received a light non-dairy breakfast at 45 minutes post-dose.
- Blood samples were obtained pre-dose, and 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 18, 24, 48, 72, and 96 hours post-dose to determine omadacycline PK parameters.
- PK parameters included area under the plasma concentration vs. time curve from 0 to infinity (AUC_{inf}), AUC_{0-24}, peak plasma concentration (C_{max}), time to peak plasma concentration (T_{max}), and elimination half-life ($t_{1/2}$).
- Individual plasma AUC_{inf} values were compared using analysis of variance (ANOVA).
- AUC_{inf} values were natural log-transformed and evaluated with a linear model containing effects for gender, elderly vs. young, and a gender by age group interaction.
- A two-sided 90% confidence interval (CI) was obtained for the ratio of geometric means between the two treatment groups. If the CI fell within the boundaries of [0.80, 1.25], then the hypothesis that the AUC_{inf} for subjects was similar between groups was supported.
- Safety was assessed from adverse events, vital signs, laboratory testing, and an electrocardiogram (ECG).

RESULTS

Study Subjects

- At baseline, demographic characteristics were similar among subjects in each study, except for the protocol-driven differences in age (**Table 1**).

Table 1. Baseline Demographic Characteristics

Study 1	Young Male Oral (N=6)	Young Female Oral (N=6)	Elderly Male Oral (N=6)	Elderly Female Oral (N=5)
Mean age, years	31	38	71	69
Age range, years	20–42	33–43	66–77	65–73
Mean weight, kg	73	71	76	63
Mean BMI, kg/m²	25	29	27	26
Caucasian, n (%)	5 (83.3)	6 (100)	6 (100)	4 (80.0)
Study 2	**Young Male IV (N=6)**	**Young Female IV (N=6)**	**Young Male Oral (N=6)**	**Young Female Oral (N=6)**
Mean age, years	26	27	26	29
Age range, years	22–32	19–36	20–35	21–39
Mean weight, kg	67	66	81	67
Mean BMI, kg/m²	23	25	26	25
Caucasian, n (%)	4 (66.7)	5 (83.3)	4 (66.7)	2 (33.3)

Study 1

- Exposure (C_{max} and AUC_{inf}) was at least 30% higher among females vs. males in both age groups (**Table 2**, **Figures 1** and **2**).
- AUC_{inf} for all males vs. all females was 9.4 mg*h/mL vs. 14.6 mg*h/mL (ratio 0.64, 90% CI: 0.52, 0.80) (**Table 3**).
- No significant difference in drug exposure was observed between young and elderly subjects.
- The AUC_{inf} ratio for all elderly vs. young subjects, was 1.13 (90% CI: 0.91, 1.41).

Table 2. Summary of PK Parameters by Age and Gender After a Single 200 mg Oral Dose of Omadacycline

	Mean (standard deviation)			
Parameter	Young Males (N=6)	Young Females (N=6)	Elderly Males (N=5)	Elderly Females (N=5)
C_{max} (mg/L)	0.59 (0.17)	0.81 (0.13)	0.51 (0.08)	0.90 (0.15)
AUC_{inf} (mg*h/L)	9.33 (2.45)	13.57 (2.66)	9.99 (2.77)	16.12 (2.84)
$T_{1/2}$ (h)	17.2 (5.1)	17.0 (1.8)	21.5 (2.7)	19.9 (1.3)
T_{max} (h)	2.4 (0.7)	3.0 (0.6)	2.3 (0.7)	2.9 (0.9)

NOTE: one elderly male subject was discontinued for protocol violation.

Figure 1. Mean Plasma Concentrations of Omadacycline After a Single 200 mg Oral Dose in Young Females and Males

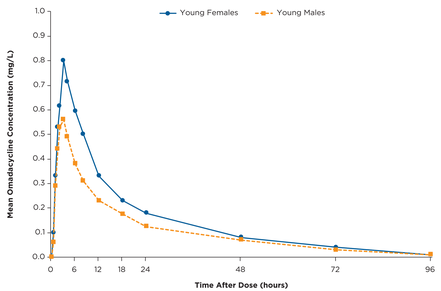


Figure 2. Mean Plasma Concentrations of Omadacycline after a Single 200 mg Oral Dose in Elderly Females and Males

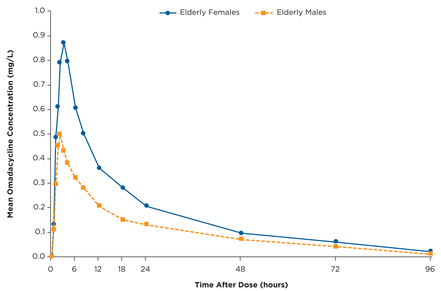


Table 3a. Least Squares Mean AUC by Age and Gender Under Fasting Conditions After a Single 200 mg Oral Dose of Omadacycline

	Young		Elderly		All Subjects	
	Males	Females	Males	Females	Males	Females
AUC_{inf} (mg*h/L)	9.00	13.35	9.73	15.89	9.36	14.57

Table 3b. Statistical Comparison of AUC by Age and Gender

Comparisons	Ratio	90% CI	ANOVA p-value
Elderly vs. young	1.13	0.91, 1.41	0.246
Male vs. female	0.64	0.52, 0.80	0.001

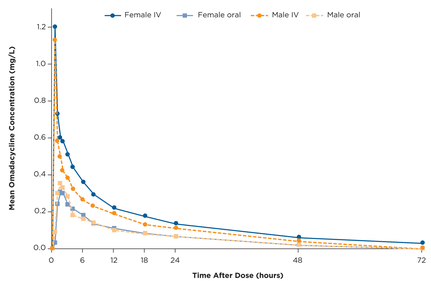
Study 2

- Compared to Study 1, a higher degree of consistency was observed for PK parameters between males and females (**Table 4**).
- After 200 mg oral administration, omadacycline exposure was similar for each gender; the AUC_{inf} ratio of males to females was 1.02 (90% CI 0.69, 1.50).
- After 100 mg IV administration, the AUC_{inf} ratio of males to females was 0.77 (90% CI: 0.67, 0.89). Though the AUC_{inf} for males was 23% lower than females, the CI range fell within the criteria for similarity.
- C_{max} was similar between males and females after either oral or IV administration (**Figure 3**).

Table 4. Bioequivalence Analysis of Omadacycline After Oral and IV Administration of 200 mg in Young Males and Females

	Geometric Least Squares (GLS) Mean				
	Male	Female	Ratio of GLS Mean for Male:Female	90% Confidence Interval	ANOVA p-value
IV – 100 mg					
C_{max} (mg/L)	1.13	1.20	0.94	0.72, 1.22	0.670
AUC_{0-24} (mg*h/L)	5.59	7.10	0.79	0.71, 0.88	0.003
AUC_{inf} (mg*h/L)	8.48	10.95	0.77	0.67, 0.89	0.008
$T_{1/2}$ (h)	16.9	16.7	0.14	-2.41, 2.70	0.922
Oral – 200 mg					
C_{max} (mg/L)	0.35	0.31	1.15	0.73, 1.80	0.597
AUC_{0-24} (mg*h/L)	2.86	3.01	0.95	0.65, 1.40	0.818
AUC_{inf} (mg*h/L)	4.37	4.29	1.02	0.69, 1.50	0.934
$T_{1/2}$ (h)	17.8	14.4	3.44	-2.21, 9.09	0.296

Figure 3. Mean Plasma Concentrations of Omadacycline After a Single 200 mg Oral or IV Dose in Young Females and Males



Safety and Tolerability

- The most frequently reported AE was nausea, which occurred only in oral dosing groups (**Table 5**).
- No subject discontinued either study for an AE.
- No serious AEs were reported in either study.
- No clinically relevant changes in vital signs, laboratory findings or ECGs were observed in either study.

Table 5. Incidence (N, %) of Treatment-Emergent Adverse Events

	Study 1	Study 2	
Adverse Event	200 mg oral (N=22)	100 mg IV (N=12)	200 mg oral (N=12)
Any event	8 (36.4)	4 (33.3)	4 (33.3)
Nausea	3 (13.6)	0	2 (16.7)
Abdominal pain	3 (13.6)	0	0
Headache	2 (9.1)	0	1 (8.3)
Diarrhea	1 (4.5)	0	0
Dizziness	0	0	1 (8.3)
Dysesthesia	0	1 (8.3)	0
Dysgeusia	0	0	1 (8.3)
Dysmenorrhea	0	1 (8.3)	0
Dysphoria	0	1 (8.3)	0
Eructation	0	0	1 (8.3)
Hyperhidrosis	0	1 (8.3)	0
Myalgia	0	1 (8.3)	0
Pharyngitis	0	1 (8.3)	0
Pyrexia	1 (2.9)	0	0
Vessel puncture site pain	0	1 (8.3)	0

SUMMARY AND CONCLUSIONS

- After administration of single doses of omadacycline 200 mg oral or 100 mg IV, female subjects tended to have higher omadacycline exposure than male subjects, though this was not observed consistently in the two studies.
- The magnitude of the differences are not clinically significant given the safety profile of omadacycline as observed in this study and across a wide range of doses in the development program.
- No effect of age on omadacycline absorption or PK profile was observed.
- Single doses of omadacycline oral and IV formulations were well tolerated; the most common AE was nausea, which occurred in 14%-17% of subjects in the oral dosing groups.
- In summary, no dosage adjustment of omadacycline is required based on patient age or gender.

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PARATEK