Pharmacokinetic-Pharmacodynamic Analyses for Alanine Aminotransferase Using Phase 3 Data From Omadacycline-Treated Patients

S.M. Bhavnani[1], M. Trang[1], D.R. George[1], K. Liolios[1], P.C. McGovern[2], L. Friedrich[2], J.N. Steenbergen[2], C.M. Rubino[1], E. Tzanis[2], P.G. Ambrose[1], J.P. Hammel[1]
[1]Institute for Clinical Pharmacodynamics, Inc., Schenectady, NY, USA;
[2]Paratek Pharmaceuticals, Inc., King of Prussia, PA, USA

ICPD INSTITUTE for CLINICAL PHARMACODYNAMICS

Sujata M. Bhavnani, PharmD., M.S., FIDSA
Institute for Clinical Pharmacodynamics, Inc.
242 Broadway
Schenectady, NY 12305
Telephone: (518) 631-8100
Fax: (518) 631-8199
E-mail: SBhavnani@ICPD.com

INTRODUCTION

- Omadacycline, an aminomethylcycline structurally related to tetracycline agents, was approved in October 2018 by the US FDA [1] for the following indications:
  - Adult patients with acute bacterial skin and skin structure infections (intravenous (IV) to oral (PO) and PO regimens); and
  - Adult patients with community-acquired bacterial pneumonia (IV-to-PO regimen).
- Tetracyclines have been associated with hepatic injury [2]. For omadacycline, elevations in ALT and AST were mostly asymptomatic, transient, of low magnitude, resolved following the completion of therapy, and did not result in discontinuation.
- To better understand exposure-related concerns for alanine aminotransferase (ALT) increase, pharmacokinetic-pharmacodynamic (PK-PD) relationships for ALT were evaluated using data from omadacycline-treated patients enrolled in three Phase 3 studies [3-5].

METHODS

- The final dataset for ALT included data from 327 omadacycline-treated patients with PK data from three Phase 3 studies.
  - For the ABSSSI studies [3,4], patients received IV followed by PO doses for one study and PO doses for the second study. For the CABP study [5], patients received IV followed by PO doses.
    - ABSSSI IV-to-PO Study (OASIS 1): Patients received omadacycline 100 mg IV every 12 hours (q12h) for 2 doses, followed by 100 mg IV every 24 hours (q24h), with the option to switch to 300 mg PO q24h after a minimum of 3 days of IV therapy, for a total duration of 7-14 days [3].
    - ABSSSI PO Study (OASIS 2): Patients received omadacycline 450 mg PO q24h for 2 doses, followed by 300 mg PO q24h for a total duration of 7-14 days [4].
    - CABP IV-to-PO Study (OPTIC): Patients received omadacycline 100 mg IV q12h for 2 doses, followed by 100 mg IV q24h, with the option to switch to 300 mg PO q24h after a minimum of 3 days of IV therapy [5].
- Repeated measures multiple linear regression was used to evaluate factors predictive of ALT, including different omadacycline total-drug area under the concentration-time curve (AUC) measures prior to each ALT, with interactions and covariates selected stepwise.
  - Using a population pharmacokinetic (PK) model and PK data from patients, different measures of omadacycline total-drug AUC, with varying time windows prior to ALT assessments, were assessed [6].
- Using a final Akaike's Information Criterion-optimized model, predicted percent probabilities of ALT elevation >1, 1.5, 2, 3, 5, and 10 x upper limit of normal (ULN) at any time post-baseline and up to two days after the end of therapy were calculated among analysis patients for fixed post-baseline omadacycline AUC measures.
- Assessments of ALT elevation endpoints across fixed post-baseline omadacycline exposures were also carried out among subsets of the analysis population defined by independent variables included in the final model or other clinically relevant variables.

METHODS

- Using final models, predicted percent probabilities of achieving ALT elevation endpoints were calculated for simulated subjects after the following FDA approved omadacycline IV and IV-to-PO dosing regimens:
  - 100 mg IV q12h on Day 1 followed by 100 mg IV q24h on Day 2, with a PO switch to 300 mg PO q24h on Day 3;
  - 200 mg IV q24h on Day 1 followed by 100 mg IV q24h on Day 2, with a PO switch to 300 mg PO q24h on Day 3; and
  - 450 mg PO q24h on Days 1 and 2, followed by 300 mg PO q24h on Day 3.

RESULTS

- The final model for ALT, developed using data from 327 patients with PK data and based on $\log_2$ALT as the dependent variable, is shown in **Table 1**.
  - This model included increased prior cumulative AUC among males (via their interaction), increased baseline gamma glutamyl transferase, and study (OASIS 2) as factors predictive of increased ALT ($p < 0.0001$).
  - The median baseline ALT (interquartile range) among patients from the OASIS 1, OASIS 2, and OPTIC was 19 (7,137), 29.1 (15.6, 141), and 20.5 (6, 122) U/L, respectively, explaining the study differences in ALT identified by the model.
  - Sex was the only independent variable for which an interaction with prior cumulative AUC was identified.

Table 1. Repeated measures multiple linear regression model for ALT with cumulative AUC evaluated as an independent variable

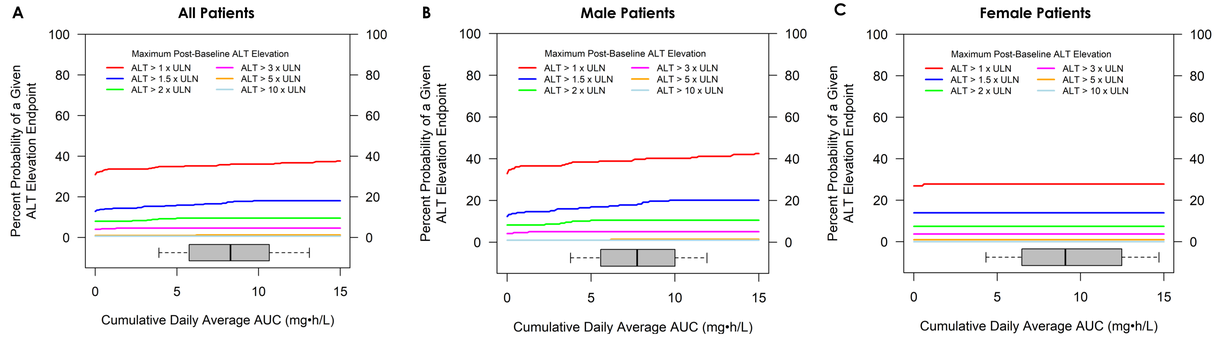
Variable	Parameter estimate	SE	Means Ratio 95% Confidence Interval	P-value
Intercept	4.094	0.1050	-	-
Cumulative AUC (mg•h/L)[a]	0.0030	0.0060	1.002 (0.995, 1.010)	0.58
OASIS 2 study in patients with ABSSSI	0.5830	0.0940	1.498 (1.318, 1.703)	<0.0001
OPTIC study in patients with CABP	0.1630	0.1280	1.119 (0.941, 1.332)	0.20
Sex (male)	0.1800	0.0910	1.133 (1.001, 1.281)	0.049
Baseline gamma glutamyl transferase (per one U/L increase)	0.0460	0.0090	1.033 (1.020, 1.045)	<0.0001
Interaction between male and cumulative AUC	0.0270	0.0070	1.019 (1.009, 1.029)	<0.0001

Model AIC = 1984.97
a. Cumulative AUC was evaluated on the square root transformation scale.

- The model-predicted impact of omadacycline across fixed cumulative daily average AUC values on ALT elevation endpoints of > 1, 1.5, 2, 3, 5, and 10 x ULN was minimal (**Figure 1A**), even for males despite the interaction with AUC (**Figure 1B**). There was virtually no estimated impact of exposure on ALT elevations among females (**Figure 1C**).
- The estimated increases in percent probabilities of the ALT elevation endpoints of > 1, 1.5, 2, 3, 5, and 10 x ULN for the 90th percentile of AUC relative to zero AUC across all patients were 5.81, 5.20, 1.53, 0.61, 0.31, and 0%, respectively, and ≤ 11.5, 7.76, 8.33, 1.31, 1.31, and 0%, respectively, across single variable patient subsets.
  - The variables on which the subsets were based included age, baseline bilirubin, body mass index, metformin use, statin use, diabetes, baseline gamma glutamyl transferase, history of liver disease, sex, study, and route of administration.

RESULTS

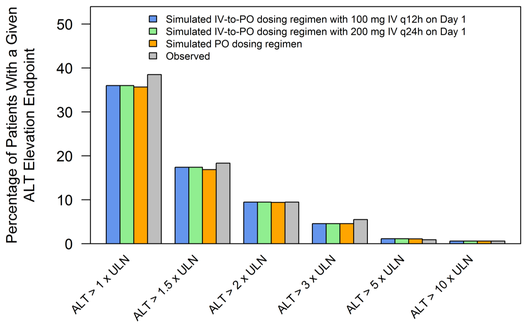
Figure 1. Model-predicted percent probabilities of achieving ALT elevation endpoints among all patients (A), and male (B), and female patients (C), respectively, across a range of cumulative daily average omadacycline AUC values[a]



a. The boxplot represents the distribution (10th, 25th, 50th, 75th, and 90th percentiles) of the cumulative daily average AUC among all post-baseline ALT observations for the specified patients in the analysis population.

- Percent probabilities of ALT elevation endpoints were within 2.84% when comparing simulated and observed patients after administration of omadacycline IV-to-PO and PO dosing regimens (**Figure 2**).

Figure 2. Percentage of ALT elevation endpoints among simulated and observed patients after administration of omadacycline IV-to-PO and PO dosing regimens



CONCLUSIONS

- A statistically significant relationship between increase in ALT and increase in omadacycline AUC for males in the presence of other factors was found.
- Increases in model-predicted ALT elevation endpoints across fixed omadacycline AUC values, or among simulated patients after administration of omadacycline IV-to-PO and PO dosing regimens relative to observed patients, were minimal, and are unlikely to be clinically meaningful in omadacycline-treated patients.

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