Safety and Tolerability of IV Omadacycline (OMC) and Tigecycline (TGC) in Healthy Subjects in a Study to Assess Intra-Pulmonary Steady-State Concentrations

Poster P1257
Abstract 5737

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ABSTRACT

Background: OMC, a first-in-class aminomethylcycline antibiotic, is currently in phase 3 development for the treatment of community-acquired bacterial pneumonia (CABP). Tigecycline, a glycylcycline, is approved for the treatment of CABP. The primary objective of this open-label phase 1 study was to assess intra-pulmonary concentrations of OMC and TGC dosed IV to steady-state in healthy subjects. This is the first clinical study to directly compare IV OMC to IV TGC dosing.

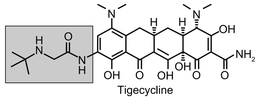
Material/methods: A total of 63 healthy subjects received OMC (n=42, 100 mg IV every 12 h for 2 doses, then 100 mg IV daily) or TGC (n=21, 100 mg IV loading dose, then 50 mg IV every 12 h). Total treatment duration was 4 days. After the last dose, bronchoalveolar lavage (BAL) was performed once per subject for pharmacokinetic analysis. Blood samples for safety hematology and chemistry were collected and a 12-lead ECG was performed prior to dosing and at the study completion visit (1 day following the last dose). Vital signs (body temperature, blood pressure, pulse rate, and respiratory rate) were measured prior to treatment, daily (pre-dose) during treatment and at study completion. In addition, blood pressure, pulse rate and respiratory rate were measured just prior to, 30 min after and 60 min after the BAL procedure. Adverse events were recorded from the signing of informed consent through the final follow-up assessment 7-14 days after the last dose.

Results: All enrolled subjects received at least one dose of study drug and were included in the evaluation for safety. Overall, 12 (28.6%) OMC subjects and 11 (52.4%) TGC subjects had at least 1 TEAE, all were considered mild to moderate in severity. The most frequent TEAEs (>1 subject in either treatment group) were headache (11.9% OMC, 14.3% TGC), epistaxis (4.8% OMC, 9.5% TGC), nausea (2.4% OMC, 47.6% TGC), decreased appetite (0% OMC, 9.5% TGC) and vomiting (0% OMC, 14.3% TGC). There were no serious adverse events reported in either treatment group during the study. Two TGC subjects discontinued study treatment and the study due to adverse events (both nausea which was considered related to study drug). No OMC subjects discontinued study treatment or the study due to adverse events. There were no clinically significant differences between the treatment groups in analyses of laboratory values, ECG parameters, or vital signs.

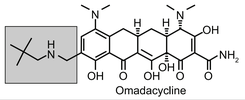
Conclusions: Over a 4-day treatment period in healthy subjects, IV OMC was associated with fewer gastrointestinal TEAEs than IV TGC.

INTRODUCTION

- Omadacycline (PTK 0796) is a first-in-class aminomethylcycline antibiotic
- Chemical structure overcomes efflux pump and ribosomal protection mechanisms of tetracycline resistance
- In vitro activity against respiratory pathogens including:
  - Methicillin-resistant *Staphylococcus aureus* (MRSA)
  - Multidrug-resistant *Streptococcus pneumoniae*
  - *Haemophilus influenzae, Moraxella catarrhalis*
  - *Legionella pneumophila, Chlamydophila pneumoniae, Mycoplasma pneumoniae*
- OMC was recently shown to be noninferior to moxifloxacin in a Phase 3 clinical trial for community-acquired bacterial pneumonia (CABP), NCT02531438[1]
- Comparison of the plasma and intrapulmonary pharmacokinetics of omadacycline and tigecycline were used to define the time course and magnitude of drug concentrations in the lung. TGC has established lung PK and approval for treatment of CABP[2]
- OMC and TGC are structurally related with key modification at C-9



Tigecycline



Omadacycline

METHODS

- Single-center, multiple-dose, open-label study in healthy subjects
  - 18-55 year-old males and females (pregnant or nursing excluded)
  - No significant past medical history
  - No concomitant medications
  - Non-smokers
- Screening period of up to 21 days, Baseline evaluation, 4 day treatment period, study completion visit on the day following last drug dose, final follow-up assessment 7-14 days following last drug dose
- Subjects were randomized to receive IV doses of OMC or TGC (both arms dosed 4 days to steady state)
- Blood samples were collected to measure drug concentration in plasma prior to and following the last drug dose
- Each subject had a single standardized bronchoscopy and bronchoalveolar lavage (BAL) procedure

Table 1. Study Procedures

	Omadacycline	Tigecycline
Dosing	100 mg IV q12h x 2 doses, then 100 mg q24h x 3 doses	100 mg IV x 1 dose, then 50 mg q12h x 6 doses
Plasma sampling	0, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 24 h after the start of the 5th dose	0, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12 h after the start of the 7th dose
BAL	Single procedure at 0.5, 1, 2, 4, 8, 12, or 24 h after the start of the 5th dose	Single procedure at 2, 4, 6, or 12 h after the start of the 7th dose

Safety Assessments

- Adverse events were recorded from the time of informed consent to the final follow-up visit
- Physical examinations
- 12-lead ECGs
- Vital signs measurements (temperature, pulse, blood pressure, respiratory rate)
- Hematology and blood chemistry

RESULTS

- The study was conducted at a single center in Phoenix, Arizona, USA. All subjects provided consent to participate using an Institutional Review Board-approved informed consent form. The study was conducted between October 2015 and April 2016
- A total of 63 subjects were enrolled and received at least one dose of study drug (42 subjects received OMC, 21 subjects received TGC). Any subject who received at least 1 dose of OMC or TGC was included in the safety population

Table 2. Demographics and Baseline Characteristics (Safety Population)

Parameter Statistic/Category	Omadacycline (N = 42)	Tigecycline (N = 21)	Overall (N = 63)
Age (years)	38.1 (9.55)	38.2 (11.16)	38.2 (10.02)
Gender, n (%)			
Male	29 (69.0)	15 (71.4)	44 (69.8)
Female	13 (31.0)	6 (28.6)	19 (30.2)
Height (cm)	173.0 (9.84)	172.2 (10.47)	172.7 (9.98)
Weight (kg)	78.28 (12.398)	78.10 (12.656)	78.22 (12.382)
BMI (kg/m^2)	26.05 (2.595)	26.24 (2.724)	26.12 (2.618)

Data are expressed as mean (standard deviation) except for gender. BMI = body mass index.

RESULTS

Adverse Events

Table 3. Overview of Adverse Events

Parameter	Omadacycline (N = 42) n (%)	Tigecycline (N = 21) n (%)	Overall (N = 63) n (%)
Total number of TEAEs	13	24	37
Subjects with at least 1:			
TEAE	12 (28.6)	11 (52.4)	23 (36.5)
Drug-related TEAE	0	11 (52.4)	11 (17.5)
Severe TEAE	0	0	0
Serious AE	0	0	0
Serious TEAE leading to death	0	0	0
TEAE leading to discontinuation of study	0	2 (9.5)	2 (3.2)
TEAE leading to discontinuation of dosing	0	2 (9.5)	2 (3.2)

AE = adverse event; TEAE = treatment-emergent adverse event.

- All TEAEs in both treatment groups were considered mild or moderate in severity. No severe or serious AEs were reported
- Overall OMC subjects experienced fewer TEAEs than TGC subjects
- No subjects in the OMC group had a TEAE that was related to study drug, while among the TGC subjects with TEAEs, all had at least 1 TEAE related to study drug

Table 4. Summary of TEAEs by SOC and PT

SOC PT	Omadacycline (N = 42) n (%)	Tigecycline (N = 21) n (%)	Overall (N = 63) n (%)
Subjects with at least 1 TEAE	12 (28.6)	11 (52.4)	23 (36.5)
GI disorders	2 (4.8)	11 (52.4)	13 (20.6)
Nausea	1 (2.4)	10 (47.6)	11 (17.5)
Salivary hypersecretion	1 (2.4)	0	1 (1.6)
Vomiting	0	3 (14.3)	3 (4.8)
Abdominal pain	0	1 (4.8)	1 (1.6)
Constipation	0	1 (4.8)	1 (1.6)
Diarrhea	0	1 (4.8)	1 (1.6)
Nervous system disorders	5 (11.9)	3 (14.3)	8 (12.7)
Headache	5 (11.9)	3 (14.3)	8 (12.7)
Respiratory, thoracic, and mediastinal disorders	3 (7.1)	2 (9.5)	5 (7.9)
Epistaxis	2 (4.8)	2 (9.5)	4 (6.3)
Nasal congestion	1 (2.4)	0	1 (1.6)
General disorders and administration site conditions	2 (4.8)	0	2 (3.2)
Infusion site pain	1 (2.4)	0	1 (1.6)
Peripheral swelling	1 (2.4)	0	1 (1.6)
Metabolism and nutrition disorders	0	2 (9.5)	2 (3.2)
Decreased appetite	0	2 (9.5)	2 (3.2)
Blood and lymphatic system disorders	0	1 (4.8)	1 (1.6)
Neutrophilia	0	1 (4.8)	1 (1.6)
Skin and subcutaneous tissue disorders	1 (2.4)	0	1 (1.6)
Hyperhidrosis	1 (2.4)	0	1 (1.6)

If a subject had more than 1 TEAE coded to the same term, the subject was counted only once. System organ class terms were sorted by descending overall frequency. Preferred terms were sorted within SOC by decreasing frequency within the omadacycline column.
AE = adverse event; GI = gastrointestinal; PT = preferred term; SOC = system organ class; TEAE = treatment emergent adverse event.

- The most commonly reported TEAE in the OMC group was headache, but this occurred with comparable incidence in both groups (11.9% OMC, 14.3% TGC)
- Gastrointestinal disorder TEAEs occurred at a higher frequency in the TGC group including nausea (2.4% OMC, 47.6% TGC) and vomiting (0% OMC, 14.3% TGC)
- Two subjects in each treatment group had epistaxis that was considered unrelated to study drug. Note that bronchoscopy procedures were performed transnasally in most subjects

RESULTS

Table 5. Discontinuations Due to Adverse Events

Parameter	Omadacycline (N = 42) n (%)	Tigecycline (N = 21) n (%)	Overall (N = 63) n (%)
Subjects with at least 1 TEAE leading to discontinuation of dosing	0	2 (9.5)	2 (3.2)
Nausea	0	2 (9.5)	2 (3.2)

- For the 2 TGC subjects who discontinued study drug due to nausea, both events were considered moderate in severity and were considered related to study drug; each subject received treatment with ondansetron

Concomitant medications

- All subjects received topical lidocaine hydrochloride for local anesthesia during the bronchoscopy procedure. Other concomitant medications are summarized in the table below

Table 6. Concomitant Medications Used During Study

Concomitant Medication	Indication	Omadacycline (N = 42) n (%)	Tigecycline (N = 21) n (%)
Acetaminophen	Headache	4 (9.5)	2 (9.5)
Zofran® (ondansetron)	Nausea or vomiting	1 (2.4)	8 (38.1)
Depo-Provera® (medroxyprogesterone acetate)	Birth control	1 (2.4)	0
Nyquil™ (medinite)	Nasal congestion	1 (2.4)	0
Miralax® (macrogol)	Constipation	0	1 (4.8)

- The most commonly administered medication was Zofran® (ondansetron) for nausea or vomiting, which was given to 8/21 (38.1%) TCG (one subject also had sharp abdominal pain) and 1/42 (2.4%) OMC subjects

Vital Signs and ECGs

- Analyses of change over time in systolic and diastolic blood pressure, heart rate, and respiratory rate revealed no clinically meaningful change in mean or median values over time, and there were no meaningful differences between treatment groups at any timepoint
- Mean and median values for 12-lead ECG parameters were similar at Baseline, Screening, and at Study Completion. No abnormal ECG finding was considered to be clinically significant by the investigator

Laboratory Data

- Overall, mean and median hematology and serum chemistry results were within the reference ranges at the timepoints assessed and the analyses of change over time revealed no clinically meaningful change in mean or median values at the study completion or early termination visits. Median changes from baseline to Day 5 for selected parameters are shown in the tables below

Table 7. Hematology

	Omadacycline (N = 42)		Tigecycline (N = 21)	
Parameter	BL	D5 Δ	BL	D5 Δ
Hemoglobin, g/L	148	2.0	141	6.0
Hematocrit, %	46	0.01	45	0.02
Leukocytes, 10^9/L	6.0	0	6.2	–0.1
Neutrophils, 10^9/L	3.4	0.1	3.2	0.2
Eosinophils, %	2.0	0	3.0	0
Platelets, 10^9/L	250	–2.0	280	–18.0

BL = median baseline value; D5 Δ = median change from baseline to Day 5.

RESULTS

Table 8. Renal and Liver Chemistry

	Omadacycline (N = 42)		Tigecycline (N = 21)	
Parameter	BL	D5 Δ	BL	D5 Δ
BUN, µmol/L	4.6	0	3.9	2.1
Creatinine, µmol/L	87.1	–2.7	97.2	–0.9
ALT, U/L	18.0	4.0	22.0	1.0
AST, U/L	19.5	0	20.0	0.5
GGT, U/L	18.0	1.0	18.0	0
Total bilirubin, µmol/L	6.8	0	6.8	0.9
Alkaline phosphatase, U/L	69.0	1.0	69.0	19.0

BL = median baseline value; D5 Δ = median change from baseline to Day 5.

CONCLUSIONS

- In this study, omadacycline was administered at the same IV dose that is being evaluated in Phase 3 trials for treatment of ABSSSI and CABP in adults. The tigecycline dose is the standard recommended adult dosage in approved prescribing information[2]
- Omadacycline was well tolerated over the 4 days of dosing in this study; gastrointestinal events were infrequent and no subjects discontinued study treatment due to adverse events
- In contrast, approximately half of the tigecycline group experienced nausea and 2 subjects (9.5%) discontinued tigecycline due to nausea
- There were no serious adverse events reported in either treatment group, and there were no clinically significant differences between the treatment groups in analyses of laboratory values, ECG parameters, or vital signs
- These findings were generally consistent with the known safety and tolerability profiles for these drugs at the studied dosing regimens as observed in prior clinical studies[2-4]
- Overall, over a 4-day treatment period in healthy subjects, IV OMC was associated with fewer gastrointestinal TEAEs than IV TGC

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