In Vitro Activity of Omadacycline Against Legionella pneumophila

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J. DUBOIS^{1*}, M. DUBOIS¹, J. –F. MARTEL¹, S. K. TANAKA²

¹ M360, Sherbrooke, Qué., Canada, ² Paratek Pharmaceuticals, Boston, MA, USA

Abstract

Background: Omadacycline (OMC) is the first aminomethylcycline in late stage clinical development for CABP and ABSSI as oral and IV, once-daily formulations. The *in vitro* activity against a variety of *L. pneumophila* isolated from 1995 to 2005 and from 2006 to 2014 was investigated to determine whether any change in susceptibility has

Methods: The *in vitro* activity of **OMC** was compared with that of doxycycline (DO), telithromycin (TE), azithromycin (AZ), erythromycin (ER), levofloxacin (LE) and moxifloxacin (MO) against a total of 50 *L. pneumophila* isolates from 1995 to 2005 (serogroup 1 (n=45) and serogroup 2, 3, 4, 5 and 6 (n=1 for each serogroup)) and against a total of 50 *L. pneumophila* isolates from 2006 to 2014 by microdilution procedure using buffered yeast extract broth containing *Legionella* growth supplement (BYE). A pre-test to determine if antibiotic activity was impacted artificially by *Legionella* supplement or iron was done by testing three ATCC quality control isolates on BYE, BYE without iron and cation-adjusted Mueller-Hinton Broth (MH).

Results: The MIC_{50/90} values of **OMC** (0.25/0.25) compared to MO (0.008/0.016), LE (0.016/0.016), TE (0.03/0.06), AZ (0.12/0.5), ER (0.12/1) and DO (1/1 mg/L) against tested *L. pneumophila* serogroup 1 isolates from 1995 to 2005 were comparable to the MIC_{50/90} values obtained by *L. pneumophila* serogroup 1 from 2006 to 2014 (**OMC** (0.25/0.25), MO (0.008/0.016), LE (0.016/0.016), TE (0.03/0.06), AZ (0.12/0.5), ER (0.25/1) and DO (1/1 mg/L)). Against all tested *L. pneumophila* isolates from 1995 to 2014, the MIC_{50/90} of MO, LE, TE, **OMC**, AZ, ER and DO was 0.008/0.016, 0.016/0.016, 0.03/0.06, **0.25/0.25**, 0.06/0.5, 0.25/1 and 1/1 mg/L respectively.

Pilot tests indicated that BYE resulted in a 5- to 7-fold increase in MICs for **OMC** and DO relative to MH for *S. aureus* ATCC29213 and *E. coli* ATCC25922. This suggests that the MIC values of **OMC** and DO obtained in BYE for *L. pneumophila* may be artificially elevated due to the media effects.

Conclusions: The activity of **OMC** has not changed between the 1995-2005 isolates and the 2006-2014 isolates. This data suggest that **OMC** may have use in infections caused by *L. pneumophila* and highlights the potential utility of this oral and IV agent for the treatment of CABP.

Introduction

Omadacycline is the first aminomethylcycline to be developed as a once daily, oral and IV treatment of Acute Bacterial Skin and Skin Structure Infection (ABSSSI) and Community-Acquired Bacterial Pneumonia (CABP). The Phase 3 development program has now been initiated. Omadacycline has excellent activity against the primary pathogens associated with ABSSSI and CABP, including antibiotic resistant organisms, including *S. aureus*, β-hemolytic *streptococci*, *S. pneumoniae*, *H. influenzae*, *Legionella* and *C. pneumoniae*.

Objective

The goal of this study was to investigate the activity of **omadacycline** against a variety of *Legionella pneumophila* isolated from 1995 to 2005 and from 2006 to 2014. We determined the minimum inhibitory concentration (MIC) of **omadacycline**, doxycycline, telithromycin, azithromycin, erythromycin, levofloxacin and moxifloxacin to evaluate whether any change in susceptibility has occurred between the two *L. pneumophila* group.

Materials and Methods

Strains

A total of 50 strains of *L. pneumophila* isolated from 1995 to 2005 (serogroup 1 (n=45) and serogroup 2, 3, 4, 5 and 6 (n=1 each serogroup)) and a total of 50 *L. pneumophila* isolates from 2006 to 2014 were collected from mostly nosocomial or acquired respiratory tract sources and were identified by standard methods such as described by Versalovic et al. (1). **Determination of MICs**

MICs were determined using the CLSI broth medium microdilution method using microdilution plating of the organisms onto a series of broth medium microplates of increasing concentrations from 0.004 mg/L to 128 mg/L (2, 3). Buffered Yeast extract (BYE) was used as the medium against *Legionella* strains. *Staphylococcus aureus* ATCC29213, *Pseudomonas aeruginosa* ATCC27853 and *L. pneumophila* ATCC33152 were included as controls.

Growth conditions

OC Strain & Media tested

S. aureus ATCC29213, E. coli ATCC25922, P. aeruginosa ATCC27853 and L. pneumophila ATCC33152 were tested in a media testing study comparing the activities of antibiotics in cation adjusted Mueller Hinton Broth (MH), standard BYE, and modified BYE ("Mod BYE"; lacking ferric pyrophosphate). Only data for E. coli and L. pneumophila is shown in Table 1.

Results

Table 1. Media Study: Susceptibility of QC strain: Escherichia coli ATCC25922 & Legionella pneumophila ATCC33152

| QC Strain & | Iviedia tested | Antibiotic MIC (mg/L) | | | | | | |
|---|--|---------------------------------------|------------------------|--------------------------------|--------------------------------|--------------------------------|--|--|
| Incubation time | | | | | | | | |
| E. coli ATCC25922 | | Omadacycline | Doxycycline | Telithromycin | Azithromycin | Erythromycin | | |
| 24 hours | Cation adjusted M-H | 1 | 2 | 32 | >128 | >128 | | |
| | Modified BYE | 16 | 0.5 | >128 | >128 | >128 | | |
| | BYE | 32 | 64 | 32 | >128 | >128 | | |
| 48 hours | Cation adjusted M-H Modified BYE BYE | Not Done 16 128 | Not Done 1 >128 | Not Done >128 128 | Not Done >128 >128 | Not Done >128 >128 | | |
| Expected MIC range | Cation adjusted M-H | 0.25-2* | 0.5-2* | Unknown | Unknown | Unknown | | |
| L pneumophila ATCC33152 | | | | | | | | |
| 24 hours | Cation adjusted M-H | No Growth | No Growth | No Growth | No Growth | No Growth | | |
| | Modified BYE | No Growth | No Growth | No Growth | No Growth | No Growth | | |
| | BYE | No Growth | No Growth | No Growth | No Growth | No Growth | | |
| 48 hours | Cation adjusted M-H Modified BYE BYE | No Growth No Growth 0.25 | No Growth No Growth | No Growth No Growth 0.03 | No Growth No Growth 0.06 | No Growth No Growth 0.25 | | |
| | | | | | | | | |
| * Expected MIC Range with Cation adjusted Mueller-Hinton, data obtained | | | | | | | | |

^{*} Expected MIC Range with Cation adjusted Mueller-Hinton, data obtained from CLSI

Results continued

Table 2. Susceptibility of *Legionella pneumophila* all tested serogroup and *L. pneumophila serogroup 1* (from 1995 to 2014; from 1995 to 2005 and from 2006 to 2014)

| | | | MIC (mg/L) | | |
|------------------------|-----------------|---------------|-------------|-------|-------|
| Organism (no. tested) | Collection Date | Antibiotic | Range | 50% | 90% |
| Legionella pneumophila | From 1995-2014 | Omadacycline | 0.06-1 | 0.25 | 0.25 |
| all serogroup | | Doxycycline | 0.5-1 | 1 | 1 |
| (100 strains) | | Telithromycin | 0.016-0.12 | 0.03 | 0.06 |
| | | Azithromycin | 0.008-0.5 | 0.12 | 0.5 |
| | | Erythromycin | 0.06-2 | 0.25 | 1 |
| | | Levofloxacin | ≤0.004-0.03 | 0.016 | 0.016 |
| | | Moxifloxacin | ≤0.004-0.06 | 0.008 | 0.016 |
| Legionella pneumophila | From 1995-2014 | Omadacycline | 0.06-0.5 | 0.25 | 0.25 |
| serogroup 1 | | Doxycycline | 0.5-1 | 1 | 1 |
| (90 strains) | | Telithromycin | 0.016-0.12 | 0.03 | 0.06 |
| | | Azithromycin | 0.016-0.5 | 0.12 | 0.5 |
| | | Erythromycin | 0.06-2 | 0.25 | 1 |
| | | Levofloxacin | ≤0.004-0.03 | 0.016 | 0.016 |
| | | Moxifloxacin | ≤0.004-0.06 | 0.016 | 0.016 |
| Legionella pneumophila | From 1995-2005 | Omadacycline | 0.06-0.5 | 0.25 | 0.25 |
| serogroup 1 | | Doxycycline | 0.5-1 | 1 | 1 |
| (45 strains) | | Telithromycin | 0.016-0.12 | 0.03 | 0.06 |
| | | Azithromycin | 0.016-0.5 | 0.12 | 0.5 |
| | | Erythromycin | 0.06-2 | 0.12 | 1 |
| | | Levofloxacin | 0.008-0.03 | 0.016 | 0.016 |
| | | Moxifloxacin | ≤0.004-0.06 | 0.008 | 0.016 |
| Legionella pneumophila | From 2006-2014 | Omadacycline | 0.06-0.5 | 0.25 | 0.25 |
| serogroup 1 | | Doxycycline | 0.5-1 | 1 | 1 |
| (45 strains) | | Telithromycin | 0.016-0.06 | 0.03 | 0.06 |
| | | Azithromycin | 0.016-0.5 | 0.12 | 0.5 |
| | | Erythromycin | 0.06-2 | 0.25 | 1 |
| | | Levofloxacin | ≤0.004-0.06 | 0.016 | 0.016 |
| | | Moxifloxacin | ≤0.004-0.06 | 0.008 | 0.016 |

Table 3. Susceptibility of *Legionella pneumophila* serogroup 2, 3, 4, 5 and 6 (from 1995 to 2014; from 1995 to 2005 and from 2006 to 2014)

| | | | MIC (mg/L) | | |
|----------------------------|-----------------|---------------|--------------|-------|-------|
| Organism (no. tested) | Collection Date | Antibiotic | Range | 50% | 90% |
| Legionella pneumophila | From 1995-2014 | Omadacycline | 0.12-1 | 0.5 | 1 |
| serogroup 2, 3, 4, 5 and 6 | | Doxycycline | 0.5-1 | 1 | 1 |
| (10 strains) | | Telithromycin | 0.016-0.06 | 0.03 | 0.06 |
| | | Azithromycin | 0.008-0.5 | 0.06 | 0.5 |
| | | Erythromycin | 0.12-1 | 0.25 | 1 |
| | | Levofloxacin | ≤0.004-0.008 | 0.008 | 0.008 |
| | | Moxifloxacin | ≤0.004-0.06 | 0.008 | 0.008 |
| Legionella pneumophila | From 1995-2005 | Omadacycline | 0.12-1 | 0.5 | 1 |
| serogroup 2, 3, 4, 5 and 6 | | Doxycycline | 1 | 1 | 1 |
| (5 strains) | | Telithromycin | 0.016-0.06 | 0.03 | 0.06 |
| | | Azithromycin | 0.008-0.5 | 0.06 | 0.25 |
| | | Erythromycin | 0.06-0.5 | 0.5 | 0.25 |
| | | Levofloxacin | 0.008 | 0.008 | 0.008 |
| | | Moxifloxacin | ≤0.004-0.008 | 0.008 | 0.008 |
| Legionella pneumophila | From 2006-2014 | Omadacycline | 0.25-0.5 | 0.25 | 0.5 |
| serogroup 2, 3, 4, 5 and 6 | | Doxycycline | 0.5-1 | 1 | 1 |
| (5 strains) | | Telithromycin | 0.016-0.06 | 0.03 | 0.06 |
| | | Azithromycin | 0.016-0.5 | 0.06 | 0.5 |
| | | Erythromycin | 0.12-1 | 0.12 | 1 |
| | | Levofloxacin | ≤0.004-0.008 | 0.008 | 0.008 |
| | | Moxifloxacin | ≤0.004-0.06 | 0.008 | 0.016 |
| | | | | | |

Discussion

jdubois@m360.ca

819.571.4366

Jacques Dubois Ph.D.

ICAAC/ICC 2015, San Diego, California

M360, Sherbrooke, Québec, Canada

- Omadacycline and doxycycline MICs were 5-7-dilution higher in BYE broth with iron, compared to broth without the iron supplement, indicating that the MIC's of omadacycline may be artificially elevated in vitro due to media effects.
- Against Legionella pneumophila all serogroups (n=100), the MICs for omadacycline ranged from =0.08 1 mg/L, and were either comparable or up to 2 dilutions lower than the most commonly used drugs for the treatment of Legionellosis, such as azithromycin and erythromycin.
- Moxifloxacin and levofloxacin are the most active compounds tested followed by telithromycin, omadacycline, azithromycin, erythromycin and doxycycline against *L. pneumophila* all serogroup, .
- Against *L. pneumophila* serogroup 1 which is the most resistant *Legionella* serogroup to erythromycin and the most usual *Legionella* serogroup isolated from respiratory tract infections, **omadacycline** (MIC $_{90}$ =0.25 mg/L) is more active than doxycycline (MIC $_{90}$ =1 mg/L), erythromycin (MIC $_{90}$ =1 mg/L) and azithromycin (MIC $_{90}$ =0.5 mg/L), .
- L. pneumophila serogroup 2, 3, 4, 5 and 6 (n=10) were less susceptible to omadacycline with a MIC₉₀ of 1 mg/L.
- Against Legionella pneumophila serogroup 2 to 6, moxifloxacin and levofloxacin still the most active compounds tested followed by telithromycin, azithromycin, erythromycin, omadacycline and doxycycline.
- Activity of omadacycline has not changed between the 1995-2005 isolates and the 2006-2014 isolates

Conclusion

Based on the *in vitro* results of this study, **omadacycline** exhibits potent extracellular activity against *L. pneumophila* and warrants further study as a potential antimicrobial agent for the treatment of pneumonia caused by *L. pneumophila*.

References

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