In Vitro and Intracellular Activity of Omadacycline Against Legionella pneumophila

**Abstract**

Background: Omadacycline (OMC) is the first aminomethylcyclohexyl in late-stage clinical development for community-acquired bacterial pneumonia (CABP), and acute skin and skin structure infection (ABSSSI). This study evaluated the in vitro, intracellular and in vivo activities of OMC against a variety of Legionella pneumophila strains isolated from nosocomial and nosocomial respiratory tract infections.

Methods: The in vitro activity of OMC was compared with that of doxycycline (DO), azithromycin (AZ), and levofloxacin (LV). The MIC range was determined by microdilution procedure using buffered yeast extract broth containing charcoal (BYE). A fresh test was used to determine if antibiotic activity was impacted artificially by Legionella. The MIC range was compared to that of DO, 0.5, 1, and 2 MIC. Legionella pneumophila ATCC27853 were grown in 24h (Day 1), 48h (Day 2), and 72h (Day 3) of incubation. The MIC range was adjusted to 10, 20, 40, and 80 MIC. The intracellular Legionella activity was performed by incubating Legionella pneumonia with amoeba at 1x the extracellular MIC of each strain during either 2 or 6 days of exposure. Counts of CFU/mL were performed daily in duplicate using the BYE agar with charcoal.

Results: After a 1 hour’s exposure of BYE broth with OMC, the CFU/mL of Legionella pneumophila ATCC27853 was 10 to 80 MIC. The MIC range of Legionella pneumophila ATCC27853 was 1, 2, 4, and 8 MIC. Both OMC and BYE were added to the Legionella pneumophila ATCC27853 cultures. After 2 days of exposure, 2, 2x, and 3x MIC and DO and 0.016, 0.032, and 0.064 MIC, respectively. The MIC range of Legionella pneumophila ATCC27853 was defined as 1, 2, 4, and 8 MIC.

Conclusions: These data demonstrate that the intracellular and extracellular Legionella activity is well controlled with OMC.

**Materials and Methods**

**Results continued**

<table>
<thead>
<tr>
<th>Strains</th>
<th>OMC (MIC)</th>
<th>DO (MIC)</th>
<th>AZ (MIC)</th>
<th>LV (MIC)</th>
</tr>
</thead>
<tbody>
<tr>
<td>S. aureus</td>
<td>ATCC29213</td>
<td>E. coli</td>
<td>ATCC25922</td>
<td>P. aeruginosa</td>
</tr>
<tr>
<td>Viable Count (CFU/mL) log10</td>
<td>1</td>
<td>2</td>
<td>4</td>
<td>8</td>
</tr>
<tr>
<td>1 day</td>
<td>1</td>
<td>2</td>
<td>4</td>
<td>8</td>
</tr>
<tr>
<td>2 days</td>
<td>1</td>
<td>2</td>
<td>4</td>
<td>8</td>
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</tbody>
</table>

**Discussion**

- Omadacycline and doxycycline MICs were 5-7 dilution higher in BYE broth with iron, compared to broth without intracellular activity. The MIC range of Legionella pneumophila isolated from respiratory tract infections, omadacycline (MIC50 = 0.25 mg/L) is more active than doxycycline (MIC50 = 1 mg/L), erythromycin (MIC50 = 1 mg/L) and azithromycin (MIC50 < 0.5 mg/L) that are commonly used drugs for the treatment of Legionella pneumophila.
- Moxifloxacin and levofloxacin are the most active compounds tested followed by omadacycline.
- Omadacycline and moxifloxacin, a significant reduction of 3 log10, CFU/ml or 99.9% of L. pneumophila serogroup 1 grown in BYE broth was reached by omadacycline and moxifloxacin after 3 days of antibiotic exposure.
- Unlike omadacycline and moxifloxacin, a significant regrowth of the intracellular Legionella pneumophila after drug washout with doxycycline, azithromycin, erythromycin, doxycycline and levofloxacin, even if we found omadacycline a regrowth of the intracellular Legionella pneumophila after drug washout with azithromycin, erythromycin, levofloxacin and levofloxacin, a modified regrowth of L. pneumophila was observed after 2 days, 3 days, 3 days and 4 days of antibiotic treatment, respectively by erythromycin, azithromycin, doxycycline and levofloxacin.

**Conclusion**

Based on the in vitro results of this study, omadacycline exhibits potent extracellular and intracellular activity against L. pneumophila serogroup 1 and warrants further study as a potential antimonial agent for the treatment of pneumonia caused by L. pneumophila.

**References**

2. Performance standards for antimicrobial susceptibility testing; 22nd Informational Supplement; M100-S22, Clinical and Laboratory Standards Institute (CLSI), Wayne, PA, January 2012.