In Vitro Intracellular Activity of Omadacycline Against Legionella pneumophila

J. Dubois, M. Dubois, J.-F. Martel, S.K. Tanka

M360, Sherbrooke, Que., Canada, 2 Paratek Pharmaceuticals, Boston, MA, USA

Abstract

Background: Omadacycline (OMC) is the first once-daily, oral and IV antimicrobials in late-stage clinical development for various community-acquired bacterial pneumonia (CABP) and acute bacterial skin and skin structure infection (ABSSSI). In vitro bacterial activity and intracellular activity using the Human Monocytes Activity (HMA) test of OMC were previously reported (Dubois et al., 2016).

Methods: The intracellular activity of OMC was compared with that of doxycycline (DO), moxifloxacin (MOX) and azithromycin (AZ) against a total of 20 L. pneumophila strains of serogroup 1. MIEC was defined as the lowest MIC (100% reduction in intracellular activity). A MIEC/MIC ratio of >0.24 (1/4XMIC) was considered robust.

Results: A total of 5 strains of L. pneumophila serogroup 1 (3 Erythromycin (ER)-resistant and 2 ER-susceptible strains) isolated from 1995 to 2014 were collected from nosocomial or acquired respiratory tract sources and were identified by standard methods such as described by Versalovic et al. (2013).

1. **Strains**
   - A total of 5 strains of L. pneumophila serogroup 1 (3 ER-resistant and 2 ER-susceptible) were tested with azithromycin, doxycycline and moxifloxacin.

2. **Results**
   - **A. S. M.** (2016) observed that the MIEC was defined as the lowest MIC (100% reduction in intracellular activity). A MIEC/MIC ratio of >0.24 (1/4XMIC) was considered robust.
   - **Objectives**
   - **Introduction**
   - Omadacycline is the first aminomuconolactone to be developed as an effective oral and IV antibiotic for the treatment of CABP caused by L. pneumophila.

3. **Materials and Methods**
   - Determination of Intracellular Human Monocytes Activity (MIEC)
   - The in vitro method using the mononuclear cells described by M.A. Horwitz (2016) was performed using human monocytes, RPMI 1640 medium (with 10% heat-inactivated fetal bovine serum), mononuclear cells (U937, 1:10 X10^6 cells/ml) and Legionella inouci (10^5 CFU/ml) were used. After a 1-hour exposure in a shaking incubator, the infected cultures were maintained under stationary conditions thereafter for 6 days at 37°C in 5% CO2 and 95% air. At Day 1 and Day 3 of antibiotic exposure, the infected cultures were washed three times. At Day 1 and Day 3 of antibiotic exposure, each strain was exposed to antimicrobial concentration of 1, 1/2, 1/4, 1/8 and 1/16 times the MIC required for omadacycline and comparators to determine the MIEC. The cultures were developed for 4 days of antibiotic exposure. Counts of CFU/ml were performed daily in triplicate using the Basal Yeast Extract agar with a MIEC/MIC ratio of >0.24 (1/4XMIC) was considered robust.

4. **Discussion**
   - Only 1 tested strain of L. pneumophila showed an important reduction (>50%) of L. pneumophila grown in macrophages at Day 3 or Day 5 of omadacycline exposure, with a MIEC/MIC ratio of 0.12 (1/8XMIC). At Day 5 of antibiotic exposure, the MIEC/MIC ratio of doxycycline, azithromycin and moxifloxacin against all L. pneumophila tested strains were similar to MIEC's obtained at Day 3 of antibiotic exposure.

5. **Conclusion**
   - Based on the in vitro results of this study, omadacycline exhibits robust bacterial activity in human monocytes and highlights the potential utility of omadacycline as an effective oral and IV antibiotic for the treatment of CABP caused by L. pneumophila.

References

3. 1* MIC curve has been obtained from Dubois et al., In vitro bacterial and Intracellular activity of Omadacycline against Legionella pneumophila; ECCMID 2016, Poster P1323.