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Paper Poster Session
Omadacycline in vitro and in vivo

In vitro bacterial and intracellular activity of omadacycline against Legionella pneumophila

Jacques Dubois*[1], Maitée Dubois[1], Jean-Francois Martel[1], Ken Tanaka[2]

[1]*M360 Inc., Sherbrooke, Canada*

[2]*Paratek Pharmaceuticals, Boston, Massachusetts, United States*

Background: Omadacycline (OMC) is the first aminomethylcycline in late stage clinical development for community-acquired bacterial pneumonia (CABP) and acute bacterial skin and skin structure infection (ABSSI) as once-daily oral and IV formulations. *In vitro* bacterial activity and intracellular activities using human monocytes against a variety of *L. pneumophila* serogroup 1 were investigated.

Material/methods: The *in vitro* activity of **OMC** was compared with that of doxycycline (DO), azithromycin (AZ), erythromycin (ER), levofloxacin (LE), and moxifloxacin (MO) against a total of 90 *L. pneumophila* serogroup 1 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 3 ATCC quality control isolates on BYE, BYE without iron, and cation-adjusted Mueller-Hinton Broth (MH). The intracellular activity of **OMC** was compared against a total of 3 ER-resistant and 2 ER-susceptible strains of *L. pneumophila* serogroup 1. The intracellular activity was determined by exposing human monocytes, U937 cell line, with intracellular *L. pneumophila* to antibiotic 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: Against tested *L. pneumophila* serogroup 1, the $MIC_{50/90}$ of MO, LE, **OMC**, AZ, ER, and DO was 0.008/0.016, 0.016/0.016, **0.25/0.25**, 0.12/0.5, 0.25/1 and 1/1 mg/L in BYE, respectively. Pilot tests suggested that the MIC values of **OMC** and DO obtained in BYE for *L. pneumophila* may be artificially elevated (5- to 7-fold increase) due to the media effects. A significant reduction of more than 3 $\log_{10}$ CFU/mL or 99.9% of ER-susceptible or ER-resistant *L. pneumophila* grown in monocytes was observed after 4 to 6 days of continuous exposure to **OMC** at 1X the MIC. A regrowth of *L. pneumophila* in monocytes was observed after 1 day of ER exposure, after 3 days of AZ and DO exposure, and after 4 days of LE exposure, however this regrowth was not observed with **OMC** and MO. After drug wash-out at day 2 of drug exposure, **OMC** followed by MO, DO, LE, and AZ, slowed substantially the regrowth of *L. pneumophila* tested strains in human monocytes, whereas a rapid regrowth occurred for ER-treated culture.

Conclusions: This data demonstrating good bacterial activity and human monocytes penetration, 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.