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Comparison of Omadacycline (OMC) and Tigecycline (TGC) Pharmacodynamics (PD) in the Plasma, Epithelial Lining Fluid (ELF), and Alveolar Macrophages (AM) in Healthy Subjects

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Background: OMC, a first in class aminomethylcycline antibiotic with activity against resistant organisms including multi-drug resistant *Streptococcus pneumoniae* and methicillin-resistant *Staphylococcus aureus* (MRSA), is currently in phase 3 development for the treatment of community-acquired bacterial pneumonia (CABP). In a murine thigh model, the optimal PD parameter for OMC and TGC was shown to be the ratio of the 24-h area under the time concentration curve to MIC (AUC_{0-24}/MIC), similar to other tetracycline-derived agents. The primary objective of this study is to compare the AUC_{0-24}/MIC for OMC and TGC in plasma, ELF, and AM in healthy volunteers.

Material/methods: Healthy adult males and females 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) to reach steady-state. Serial plasma concentrations of OMC and TGC were acquired in all subjects after the last dose. Bronchoalveolar lavage (BAL) was performed once per subject in order to obtain concentrations of either OMC or TGC in ELF and AM. AUC_{0-24} values were calculated from mean concentrations in plasma, ELF, and AM. MIC_{90} values from recent isolates of *S. pneumoniae* and

methicillin-susceptible *S. aureus* (MSSA) (each 0.12 mcg/mL for OMC and TGC), MRSA (0.25 mcg/mL for OMC, 0.12 mcg/mL for TGC), and *Legionella pneumophila* (0.25 mcg/mL for OMC, 8 mcg/mL for TGC) were used for PD analyses.

Results: Subjects who had complete data for plasma, ELF, and AM concentrations were included for analyses (OMC=41/42, TGC=17/21). The $AUC_{0\text{-}24}$/MIC values for OMC were greater than TGC at all sites evaluated. In the plasma, the $AUC_{0\text{-}24}$/MIC for OMC was 3.2-fold higher (97.8 vs 30.8) for *S. pneumoniae* and MSSA, and 1.5-fold higher (46.9 vs 30.8) for MRSA. In the ELF, the $AUC_{0\text{-}24}$/MIC for OMC was 2.7-fold higher (143.6 vs 52.7) for *S. pneumoniae* and MSSA, and 1.3-fold higher (68.9 vs 52.7) for MRSA. In the AM, the $AUC_{0\text{-}24}$/MIC for OMC was 126-fold higher (1209.8 vs 9.6) for the intracellular pathogen *L. pneumophila*.

Conclusions: The $AUC_{0\text{-}24}$/MIC for OMC exceeded that of TGC in the plasma, ELF, and AM for CABP organisms, including *S. pneumoniae*, MSSA, MRSA, and *L. pneumophila*. Higher exposure in plasma and ELF of OMC allowed for $AUC_{0\text{-}24}$/MIC values greater than TGC, even when the OMC MIC_{90} was higher. OMC has favorable pharmacokinetics at intrapulmonary sites, with ELF and AM concentrations to support the PD activity against extracellular and intracellular pathogens encountered in CABP.