P1324
Paper Poster Session
Omadacycline in vitro and in vivo

Effects of omadacycline on gut microbiota populations and Clostridium difficile germination, proliferation and toxin production in an in vitro model of the human gut

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Background: Omadacycline is a potent aminomethycycline antibiotic with activity against Gram-positive bacteria, including MSSA/MRSA and *S. pneumoniae*, Gram-negative , and atypical bacteria. It is currently in phase 3 clinical trials for acute bacterial skin and skin structure infections and community-acquired bacterial pneumonia. We have used a well validated, clinically reflective model of the human gut to investigate the effects of omadacycline exposure on the normal gut microbiota, and subsequent potential for induction of simulated *C. difficile* infection (CDI).

Material/methods: A triple stage chemostat gut model was inoculated with a pooled human faecal slurry (n=5) from healthy volunteers (age ≥60 years) and left for 2 weeks to allow bacterial populations to equilibrate. The model was challenged with 10^7 cfu/mL *C. difficile* spores (ribotype 027) on days 14 and 21. Omadacycline instillation 430 mg/L, once daily, for 7 days commenced on day 21. The model was observed for a further three weeks post-antimicrobial (days 28-49). Gut microflora populations and *C. difficile* total viable counts and spore counts were enumerated daily by culture on selective and non-selective agars. Toxin was detected by cell cytotoxicity assay, and antimicrobial concentrations were measured by bioassay.

Results: Prior to antimicrobial exposure, gut microbiota populations were stable. Omadacycline instillation caused changes to the microbiota. Declines were observed in populations of clostridia (~6 $\log_{10}$ cfu/mL), bifidobacteria (~6 $\log_{10}$ cfu/mL), *B. fragilis* group species (~3 $\log_{10}$ cfu/mL), *Lactobacillus* spp.(~2 $\log_{10}$ cfu/mL) and *Enterococcus* spp. (~4 $\log_{10}$ cfu/mL), but did not disrupt the overall population of Enterobacteriaceae. Despite these changes, no evidence of *C. difficile* germination, vegetative cell proliferation or toxin production was observed.

Conclusions: Omadacycline exposure caused marked disruption to gut microflora populations. However, in contrast to many other antimicrobials previously evaluated in the gut model (e.g. clindamycin, cefotaxime, ceftriaxone, and three fluoroquinolones), omadacycline did not promote *C. difficile* proliferation or simulated CDI. Human *in vivo* data are required to confirm the observed low potential of omadacycline to induce CDI.