27th ECCMID Vienna, Austria 22 – 25 April 2017
The congress of ESCMID

Session: P066 Various agents against Gram-positive bacteria

Category: 5a. Mechanisms of action, preclinical data & pharmacology of antibacterial agents

24 April 2017, 12:30 - 13:30
P1335

Lefamulin is highly active in-vitro against multi-drug-resistant mycoplasma genitalium strains

Jorgen Skov Jensen[1], Susanne Paukner*[2]

[1]*Statens Serum Institut; Microbiology and Infection Control*

[2]*Nabriva Therapeutics Ag; Microbiology*

Background: *Mycoplasma genitalium* is an important cause of sexually transmitted infections (STIs) accounting for approximately 25% of non-chlamydial-non-gonococcal urethritis, 15-20% of cervicitis and 10-15% of pelvic inflammatory disease. First-line treatment is azithromycin, but rates of resistance are increasing globally. Moxifloxacin is the only effective second-line therapy but mutation rates in the quinolone-resistance-determining-region (QRDR) of ParC as high as 47% have been reported from Japan. A significant proportion of the strains have dual resistance to macrolides and fluoroquinolones making treatment options extremely limited. Thus, alternative therapies for which there is no cross-resistance are urgently needed.

Pleuromutilin antibiotics inhibit bacterial growth by binding to the peptidyl transferase centre of the 50S ribosomal subunit, blocking protein synthesis, and have been used to treat mycoplasma infections in swine and poultry for decades. Lefamulin is the first semi-synthetic pleuromutilin antibiotic for IV and oral use in humans. It is currently in Phase 3 trials for the treatment of community-acquired bacterial pneumonia.

Material/methods: We evaluated the in vitro activity of lefamulin against a collection of 41 *M. genitalium* strains including the ATCC G37 type strain, 20 macrolide-susceptible clinical isolates obtained between 1980 and 2006, and 20 macrolide resistant clinical isolates obtained between 2003 and 2014. Of the 41 strains, eight were moxifloxacin resistant with seven of these also having combined macrolide resistance, thus characterised as multi-drug-resistant (MDR).

MICs were determined using the Vero cell culture and quantitative real-time PCR method. MIC was defined as the minimal antibiotic concentration that caused a 99% inhibition of growth when compared

with the mean growth of three control wells. As comparators, azithromycin, moxifloxacin, and doxycycline were included.

Results: Lefamulin was by far the most active compound with an MIC_{90} of 0.063 mg/L compared with azithromycin (MIC_{90} of 16 mg/L), moxifloxacin (MIC_{90} of 8 mg/L), and doxycycline (MIC_{90} of 1 mg/L). When tested against the macrolide-resistant strains (azithromycin MIC of >8 mg/L) lefamulin had an MIC_{90} 0.063 mg/L (range 0.002-0.063 mg/L) while against the macrolide-susceptible subset the MIC_{90} was 0.0016 mg/L (p=0.002). Lefamulin MICs against the seven MDR strains which were resistant to macrolides and fluoroquinolones were similar to those of the macrolide-resistant and moxifloxacin-susceptible strains (MIC_{90} 0.063 mg/L for both groups).

Conclusions: Lefamulin was highly active against all *M. genitalium* strains tested regardless of their macrolide and moxifloxacin resistance phenotype. With the growing problems of MDR *M. genitalium* strains, particularly in the Asia-Pacific region, further evaluation of lefamulin in a clinical trial is warranted.