P0247

Paper Poster Session I

New antibacterial drugs

In vitro and *in vivo* efficacy of novel extended-spectrum pleuromutilins against *S. aureus* and *S. pneumoniae*

S. Paukner[1], W. Wicha[1], K. Thirring[1], H. Kollmann[1], Z. Ivezic-Schoenfeld[1]

[1]*Nabriva Therapeutics, Vienna, Austria*

Objective

Resistance development to antibiotics imposes a growing public health threat worldwide. In Europe particularly the resistance of *E. coli* and *K. pneumoniae* against cephalosporins, fluoroquinolones and aminoglycosides increased significantly while the percentage of MRSA was decreasing during the last few years. Nevertheless, MRSA remains above 25 % in almost one fourth of the reporting countries and is one of the most frequent causes of antibiotic-resistant healthcare-associated infections worldwide (ECDC, 2013). Thus the need for new antibiotics acting against those pathogens is evident.

The recently discovered extended spectrum pleuromutilins (ESP) address this problem by being active against Gram-negative and -positive bacteria. This study investigated the *in vitro* activity of four novel ESP derivatives against *S. aureus* (MSSA, MRSA) and *S. pneumoniae* including multi-resistant isolates. Furthermore, the ESP derivatives were evaluated in an initial *in vivo* efficacy model in mice infected with *S. aureus* to proof their therapeutic potential in comparison to linezolid and tigecycline.

Methods

MICs of ESP and comparators against MSSA (*n* = 25), CA-MRSA (*n* = 20) and *S. pneumoniae* (*n* = 32) were determined by broth microdilution according to CLSI (M7/A9).

To evaluate the therapeutic potency of the selected ESPs *in vivo*, mice were infected intraperitoneally with an inoculum of approximately 4×10^7 CFU MSSA per mouse causing a lethal sepsis within 24 h. The drugs were administered s.c. as single dose 1 h post infection and survival was recorded for 96 h. The total daily dose required for survival of 50 % of mice (ED_{50}) and 95 % confidence limits were calculated by binary probit analysis.

Results

The tested ESP derivatives BC-7634, BC-9074, BC-9529, and BC-9563 showed potent antibacterial activity against MSSA and CA-MRSA including predominantly USA300 strains with MIC_{90} of ≤ 0.25 µg/mL. Against *S. pneumoniae* ESPs displayed MIC_{90} values of 0.25-0.5 µg/mL. The activity was unaffected by resistance to macrolides, tetracyclines, or cephalosporins.

In the *S. aureus* bacteremia model all selected ESPs showed good *in vivo* efficacy when compared to linezolid and tigecycline. BC-7634, BC-9074, BC-9529, and BC-9563 showed ED_{50} values of 0.26 mg/kg/day, 0.57 mg/kg/day, 0.47 mg/kg/day and 0.14 mg/kg/day, respectively. Linezolid and tigecycline had ED_{50} values of 10.3 mg/kg/day and 0.99 mg/kg/day, respectively.

Conclusion

The novel ESPs showed potent activity against *S. aureus* (MSSA and CA-MRSA) and *S. pneumoniae*. In a murine bacteremia caused by *S. aureus* all tested ESP showed good efficacy being as active as tigecycline and significantly more active than linezolid. These proof-of-concept studies warrant the further development of ESP since the antibacterial spectrum does not only cover resistant *Enterobacteriaceae* but ESPs additionally demonstrate potent activity against Gram-positive pathogens.