In-vitro activity of plazomicin against colistin-resistant Enterobacteriaceae including plasmid-encoded MCR-1-producing isolates

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**Background:** Plazomicin is a next-generation aminoglycoside that was developed to overcome common aminoglycoside-resistance mechanisms. Plazomicin is under development to treat patients with serious bacterial infections due to MDR Enterobacteriaceae, including ESBL-producing and carbapenem-resistant Enterobacteriaceae. Resistance to colistin, a last line agent used to treat these infections, is increasing. We evaluated the activity of plazomicin and comparators against 95 colistin-resistant clinical Enterobacteriaceae isolates.

**Material/methods:** A total of 95 colistin-resistant clinical Enterobacteriaceae isolates collected from ten hospitals in eight countries were susceptibility tested against plazomicin and comparators using CLSI broth microdilution methods. 42 isolates (Klebsiella pneumoniae and K. oxytoca) possessed defined chromosomal colistin-resistance mechanisms (eg mgrB, phoPQ or pmrAB mutations), 21 isolates expressed mcr-1 (Escherichia coli and Salmonella enterica), 8 isolates were...
intrinsically resistant to colistin (eg. *Serratia*, *Proteus*, *Providencia*, and *Hafnia* spp) and 24 isolates (*K. pneumoniae*, *E. coli* and *Enterobacter* spp.) had undefined, non-*mcr-1* colistin resistance mechanisms. Susceptibility profiles were defined according to CLSI with the exception of colistin, where EUCAST breakpoint criteria were applied.

**Results:** Plazomicin inhibited 89.5% and 93.7% of the Enterobacteriaceae isolates at ≤2 and ≤4 µg/mL, respectively. Plazomicin MICs were ≤2 µg/mL against all of the *mcr-1* positive isolates and ≤4 µg/mL against all of the phenotypic colistin resistant Enterobacteriaceae. Non-susceptibility to currently marketed aminoglycosides was common with 16.8%, 47.4% and 63.2% of the isolates non-susceptible to amikacin, gentamicin and tobramycin, respectively. Plazomicin was the most potent aminoglycoside tested with a MIC<sub>90</sub> of 4 µg/mL compared to 32 µg/mL, > 64 µg/mL and 64 µg/mL for amikacin, gentamicin and tobramycin, respectively.

**Conclusions:** Plazomicin displayed potent in vitro activity against colistin-resistant clinical Enterobacteriaceae isolates, including those expressing the *mcr-1* gene. The activity of plazomicin was greater compared to other aminoglycosides against this collection of isolates. The further development of plazomicin for the treatment of infections due to MDR Enterobacteriaceae, including those strains with colistin resistance is warranted.