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P0093 Plazomicin activity against Enterobacteriaceae collected from Europe, Latin America, and Asia-Pacific during 2016, including those with aminoglycoside and beta-lactam resistance mechanisms

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Background: Plazomicin, a next-generation aminoglycoside, was developed to overcome common aminoglycoside-resistance mechanisms. We evaluated plazomicin activity against *Enterobacteriaceae* clinical isolates collected in Europe (n=2,045), Latin America (n=511), and Asia-Pacific (n=682) during 2016 and evaluated aminoglycoside and beta-lactam resistance mechanisms among these isolates.

Materials/methods: A total of 3,238 *Enterobacteriaceae* were susceptibility tested using the reference broth microdilution method. ESBL-phenotype, carbapenem-resistant *Enterobacteriaceae* (CRE), and isolates resistant to ≥1 aminoglycoside were screened for resistance genes using whole genome sequencing analysis.

Results: Plazomicin ($MIC_{50/90}$, 0.5/1 mg/L) inhibited 96.3% and 98.2% of the *Enterobacteriaceae* at ≤2 mg/L and ≤4 mg/L, respectively. Amikacin, gentamicin, and tobramycin inhibited 94.3%, 82.1%, and 75.9% of these isolates, respectively (EUCAST breakpoints). Plazomicin displayed activity against *E. coli* (n=1,182; $MIC_{50/90}$, 0.5/1 mg/L), *K. pneumoniae* (n=1,115; $MIC_{50/90}$, 0.25/0.5 mg/L), and *E. cloacae* (n=56; $MIC_{50/90}$, 0.25/0.5 mg/L). Plazomicin ($MIC_{50/90}$, 0.25/1 mg/L) inhibited 94.6% and 94.8% of the 688 isolates carrying ESBL genes at ≤2 mg/L and ≤4 mg/L, respectively. The most common ESBL genes were $bla_{CTX\text{-}M\text{-}15}$ (n=486) and $bla_{CTX\text{-}M\text{-}14}$ (n=51). Plazomicin inhibited 78.8% of the 170 CRE at ≤2 mg/L or ≤4 mg/L. Other aminoglycosides inhibited 14.1% to 48.8% of these isolates (EUCAST breakpoints). Carbapenemase genes were found in 138 CRE isolates and included 74 bla_{KPC}, 39$bla_{OXA\text{-}48}$-like, and 26 $bla_{NDM\text{-}1}$. Aminoglycoside-modifying enzymes (AME) were observed among 630/644 isolates tested and the most common genes were *aac(6')-Ib-cr* (n=352) and *aac(3)-IIa* (n=312). Plazomicin ($MIC_{50/90}$, 0.5/2 mg/L) inhibited 92.7% and 93.5% of the AME-carrying isolates at ≤2 mg/L and ≤4 mg/L, respectively. Amikacin, gentamicin, and tobramycin inhibited 75.1%, 17.5%, and 1.7%, respectively, of these isolates using the EUCAST breakpoints. 16S rRNA methylases were detected in 48/644 isolates, and these isolates were resistant to all AMGs; plazomicin MIC values were ≥128 mg/L. One *Providencia stuartii* isolate was highly resistant to all aminoglycosides, including plazomicin, and carried *aac(2')-Ia*.

Conclusions: Plazomicin was active against the *Enterobacteriaceae* tested, including ESBL- and AME-carrying isolates and approximately 80% of the CRE. Our results support the development plan

for plazomicin to treat serious infections caused by resistant *Enterobacteriaceae* when treatment options are limited.

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