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Comparative in-vitro activity of Eravacycline, a novel fluorocycline, against mcr-1-positive Escherichia coli and Klebsiella pneumoniae

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Background: Eravacycline (ERV, Tetraphase Pharmaceuticals) is a novel, fully-synthetic fluorocycline antibiotic designed to overcome acquired mechanisms of resistance against tetracycline-class antibiotics (active drug efflux & ribosomal protection), ERV may have a role in the treatment of multidrug- (MDR) and extensively drug-resistant (XDR) Gram-negative (GN) pathogens carrying an array of acquired resistance determinants e.g.,*mcr-1*, bla_{NDM}, bla_{VIM}, bla_{KPC}, $bla_{OXA\text{-}like}$. The newly described mobile gene, *mcr-1*, conveys transferable resistance to polymyxin-class antimicrobials, including colistin (COL). Given the role of COL as a last-line therapeutic against MDR GN infections, coexistence of *mcr*-1 alongside other resistance phenotypes is of great concern. Herein we present the evaluation of ERV as a viable therapeutic option against 100 *mcr-1*-positive, COL-resistant *Enterobacteriaceae*.

Material/methods: Presence of *mcr-1* was confirmed in *E. coli* (n=81) and *K. pneumoniae* (n=19) isolates of diverse origins using standard PCR methodology with the following primers; 5'-cgg tcagtccgtttg ttc-3' and 5'-ctt ggtcggtctgta ggg-3'.Minimal inhibitory concentration (MIC) values for ERV and comparator antibiotics (see Table 1) were determined using standardised microbroth dilution assays. Results were interpreted using EUCAST guidelines.

Results: MIC_{90} values of the comparator antibiotics against *mcr-1*-positive *E. coli* were above resistance breakpoints, with ertapenem (ERT) the only exception. In comparison, ERV MIC_{50} and MIC_{90}values were 0.25µg/ml and 0.5µg/ml, respectively (Table 1).Comparison of all three tetracycline antibiotics shows favourable activity of ERV against *mcr*-1-positive *E. coli*. ERV was more active

against *mcr-1*-producing *E. coli* than *K. pneumoniae*. Against *K. pneumonia,* ERV showed $MIC_{50/90}$ values of 2µg/ml, favourable to that of other tetracycline-class antibiotics tested; however, the sample size remains small to draw solid conclusions regarding MIC_{90} values.

Conclusions: ERV retained potency against COL-resistant, *mcr-1*-positive *E. coli* and *mcr-1*-positive *K. pneumoniae***.** In addition, ERV demonstrated the lowest MIC_{50} values and MIC_{90} values among the three tetracyclines included in this panel. Our results support the therapeutic potential of ERV against MDR GN bacteria, including those carrying the mcr-1 gene.

Antibiotic	***E. coli***		***K. pneumoniae***		***Antibiotic***	***E. coli***		***K. pneumoniae***	
	MIC_{50}	***MIC_{90}***	***MIC_{50}***	***MIC_{90}***		***MIC_{50}***	***MIC_{90}***	***MIC_{50}***	***MIC_{90}***
Eravacycline	0.25	0.5	2	2	**Cefepime**	8	>8	0.06	0.25
Tetracycline	>8	>8	>8	>8	**Ceftazidime**	>8	>8	0.25	>8
Tigecycline	1	2	4	4	**Cefotaxime**	>2	>2	0.06	0.125
Colistin	>2	>2	>2	>2	**Gentamicin**	2	>8	0.5	0.5
Ertapenem	0.125	0.5	0.06	0.125	**Pip/Tazo**	4	32	4	16
Levofloxacin	0.5	>2	2	2					

Table 1: MIC_{50} & MIC_{90} of mcr-1-positive E. coli (n=81) & K. pneumoniae (n=19) against eravacycline and comparator antimicrobials.