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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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Introduction

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) a last line therapeutic against MDR infections. Coexistence of *mcr*-1 alongside other resistance phenotypes, and the arise of truly pan-resistant pathogens, is now of great concern. Herein we present the evaluation of ERV as a viable therapeutic option against 100 *mcr*-1-positive, COL-resistant MDR-*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

MIC values for ERV and comparator antibiotics (see Table 1) were determined using standardised microbroth dilution assays. Results were interpreted using EUCAST guidelines.

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

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

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 0.25 µg/ml and 0.5 µg/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*.

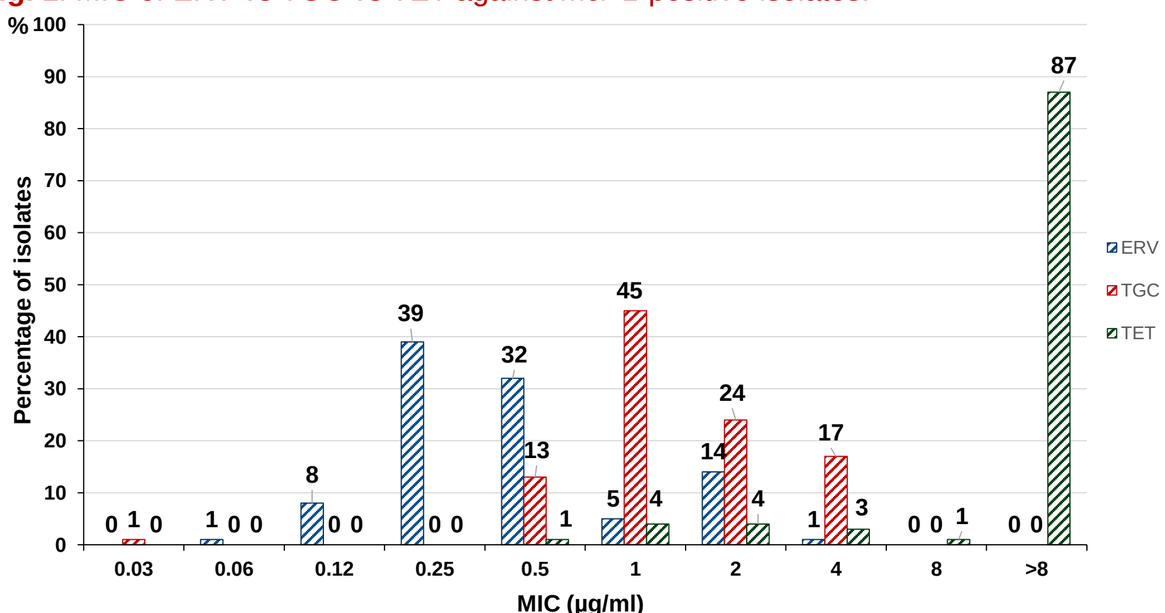
Against *K. pneumoniae*, ERV showed $MIC_{50/90}$ values of 2 µg/ml, favourable to that of other tetracycline-class antibiotics tested; however, the sample size remains small to draw solid conclusions regarding MIC_{90} values.

As shown in Fig. 1, ERV MIC values were ≤ 0.5 µg/ml against 79% of tested isolates. Tigecycline (TGC) MIC range were ≤ 4 - ≥ 1 µg/ml (86% of tested isolates) while tetracycline (TET) showed MIC values of >8 µg/ml against 87% of tested isolates.

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.

Fig. 1: MIC of ERV vs TGC vs TET against *mcr*-1-positive isolates.



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