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Eravacycline, a novel fluorocycline, has antibacterial activity against carbapenem-resistant *Enterobacteriaceae* (CRE) & *Acinetobacter* spp. (CRA)

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Introduction

Carbapenem resistant *Enterobacteriaceae* (CRE) and *Acinetobacter* (CRA) exhibit extremely drug resistant (XDR) and occasionally pan-drug resistant (PDR) phenotypes, compromising successful treatment and clinical outcome for the patient. Colistin is now considered to be the final drug capable of treating such infections; however, strains are now being isolated that are resistant to this antibiotic as well. The antibiotic 'pipeline' is dry, ergo the pursuit of new antibiotic discovery and/or modification of already existing compounds has never been more pertinent in the battle against these multidrug-resistant infections. Eravacycline (ERV, Tetraphase Pharmaceuticals) is a novel fully-synthetic fluorocycline antibacterial agent that retains activity against the most common acquired tetracycline-specific resistance mechanisms. Herein we evaluate the activity of ERV against 200 CRE and 104 CRA isolates.

Material/methods

A global selection of CRE & CRA → MICs for ERV and selected comparator antibiotics (Table1), were determined using microbroth dilution assays. Results were interpreted using EUCAST guidelines.

Table1: $MIC_{50/90}$ values of CRE (n=200) and CRA (n=104) against Eravacycline and comparator antimicrobials.

	CRE									CRA
	Total			*K. pneumoniae*			*E. coli*			
	NDM	VIM	OXA-48	NDM	VIM	OXA-48	NDM	VIM	OXA-48	
Eravacycline	0.5 / 2	0.5 / 2	0.5 / 2	0.5 / 2	0.5 / 2	1 / 2	0.25 / 1	0.25 / 1	0.125/ 0.25	0.5 / 4
Tigecycline	2 / 8	4 / 8	2 / 4	4 / 8	4 / 8	4 / 4	2/ 8	2/4	1 / 2	4 / 8
Tetracycline	>8 / >8	4 / >8	8 / >8	>8 / >8	4 / >8	8 / >8	>8 / >8	>8 / >8	>8 / >8	4 / >8
Minocycline	-	-	-	-	-	-	-	-	-	0.5 / 4
Colistin	0.5 / >2	0.5 / 1	0.5 / >2	0.5 / 1	0.5 / 1	1 / >2	0.5 / 0.5	0.5 / 0.5	1 / >2	1 / 4
Cefepime	>8 / >8	>8 / >8	>8 / >8	>8 / >8	>8 / >8	>8 / >8	>8 / >8	>8 / >8	>8 / >8	>16 / >16
Ceftazidime	>8 / >8	>8 / >8	>8 / >8	>8 / >8	>8 / >8	>8 / >8	>8 / >8	>8 / >8	>8 / >8	>32 / >32
Cefotaxime	>2 / >2	>2 / >2	>2 / >2	>2 / >2	>2 / >2	>2 / >2	>2 / >2	>2 / >2	>2 / >2	-
Gentamicin	>8 / >8	8 / >8	>8 / >8	>8 / >8	2 / >8	>8 / >8	>8 / >8	8 / >8	4/ >8	-
Amikacin	-	-	-	-	-	-	-	-	-	32 / >32
Levofloxacin	>2 / >2	2 / >2	>2 / >2	>2 / >2	1 / >2	>2 / >2	>2 / >2	>2 / >2	>2 / >2	8 / >8
Meropenem	-	-	-	-	-	-	-	-	-	>16 / >16
Ertapenem	>2 / >2	>2 / >2	>2 / >2	>2 / >2	>2 / >2	>2 / >2	>2 / >2	>2 / >2	>2 / >2	-
Pip/Tazo	>64 / >64	>64 / >64	>64 / >64	>64 / >64	>64 / >64	>64 / >64	>64 / >64	>64 / >64	>64 / >64	>128 / >128

Results

CRE genotypes were: bla_{NDM}-positive (60%), bla_{OXA-48}-positive (26%) and bla_{VIM}-positive (15%). CRA genotypes were bla_{NDM}-positive (79%), bla_{OXA-48}-positive (2%), bla_{VIM}-positive (2%) and undefined metallo-β lactamases (MBL) (17%).

In the case of CRE, ERV recorded MIC_{50} and MIC_{90} of 0.5 µg/ml and 2µg/ml respectively; possessing better antibacterial activity than all antibiotics tested (**Table 1**). For CRA, ERV also was favourable with regard to all antibiotics tested with MIC_{50} and MIC_{90} values of 0.5µg/ml and 4µg/ml, respectively. ERV was more potent than any other tested antibiotics against CRE and CRA.

ERV was the most active antibiotic against NDM- positive-CRE with $MIC_{50/90}$ values of 0.5/ 2 µg/ml. ERV also showed the lowest MIC_{50} values (0.25µg/ml) in case of NDM-positive and VIM-positive *E. coli.* ERV is particularly effective against both OXA-48-positive *E. coli and K. pneumoniae* with lowest recorded $MIC_{50/90}$ values of 0.125/ 0.25 µg/ml and 1/ 2 µg/ml respectively.

Conclusions

- ERV shows considerable activity against both CRE & CRA, and is more potent *in vitro* than any other antibiotic comparators.
- ERV has the potential to be a promising empirical treatment option for complicated hospital /health-care associated infections.

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