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Assessment of Eravacycline against a Recent Global Collection of 4,462 *Enterobacteriaceae* Clinical Isolates (2013-2014)

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Abstract

Background: Eravacycline is a novel, fully synthetic fluorocycline antibiotic with broad-spectrum activity available in intravenous and oral formulations for the treatment of multidrug-resistant (MDR) infections, including MDR Gram-negative bacteria. Eravacycline has completed enrollment in Phase 3 studies for the treatment of complicated intra-abdominal infections (cIAI) and complicated urinary tract infections (cUTI).The current study assessed the activity of eravacycline against 4,462 *Enterobacteriaceae* collected worldwide.
Methods: A total of 4,462 *Enterobacteriaceae* clinical isolates (collected from 2013-2014) were tested. MICs were determined by CLSI broth microdilution. Quality control testing was performed on each day of testing as specified by the CLSI. Susceptibility was assessed using CLSI breakpoints except for tigecycline where FDA breakpoints were used.
Results: Results are shown in the following Table:

	MIC (µg/ml)				
	MIC_{50}	MIC_{90}	%S*	%I	%R
Eravacycline	0.5	2	-	-	-
Tetracycline	2	> 8	59.8	6.6	33.6
Tigecycline	0.5	2	91.1	7.3	1.6
Aztreonam	≤ 0.5	> 16	84.7	1.3	14.1
Cefepime	≤ 0.25	2	94.8	1.5	3.7
Ceftazidime	≤ 0.5	> 16	85.3	1.1	13.5
Ceftriaxone	≤ 0.5	32	80.3	2.0	17.7
Colistin	1	> 4	-	-	-
Gentamicin	0.5	4	91.5	1.0	7.5
Imipenem	0.5	4	72.0	16.8	11.3
Levofloxacin	≤ 0.25	> 4	86.8	1.9	11.3
Piperacillin/tazobactam	2	32	87.4	9.0	3.6

*%S, I, R; percent susceptible, intermediate or resistant

Conclusions: Against a total of 4,462 *Enterobacteriaceae* clinical isolates, eravacycline exhibited the lowest MIC_{90} of 2 µg/ml (equal to cefepime and tigecycline). Eravacycline exhibited excellent activity against the majority of isolates and shows promise for the treatment of infections caused by *Enterobacteriaceae*. Data from the recently completed Phase 3 trials will be used in determining the clinical breakpoints.

Introduction

Eravacycline is a novel, fully synthetic fluorocycline antibiotic with broad-spectrum activity available in intravenous and oral formulations for the treatment of multidrug-resistant (MDR) infections, including those caused by MDR Gram-negative bacteria. Eravacycline was investigated in Phase 3 studies for the treatment of complicated intra-abdominal infections (cIAI) and complicated urinary tract infections (cUTI).

The current study assessed the activity of eravacycline against a large collection of recent clinical isolates of *Enterobacteriaceae* from both the USA and Europe.

Methods

A total of 4,462 *Enterobacteriaceae* clinical isolates (collected from 2013-2014) were tested. The majority were from body fluid sources (n = 1277, 27.6% of total), genito-urinary sources (n = 1113, 24%), gastro-intestinal sources (n = 1,094, 23.7%), respiratory sources (n = 545, 11.8%) and skin (n = 359, 7.8%). The remainder were from other sources that included blood, bone, head/ear/nose/throat, lymph, muscle and medical devices (catheters, tubes).

Minimum inhibitory concentration (MIC) endpoints were determined by broth microdilution according to CLSI guidelines (1).

Quality control testing was performed each day of testing as specified by the CLSI using *Escherichia coli* ATCC 25922 and ATCC 35218.

Antibiotic susceptibility was determined using CLSI 2015 breakpoints (2), with the exception of tigecycline where FDA breakpoints were used (3).

Results

Table 1. Summary of *Enterobacteriaceae* species and geographical origin

Organism	Number of isolates from country:																								Grand Total
	AT	BE	CZ	DK	FR	DE	EL	HU	IE	IT	LV	NL	PL	PT	RO	RU	RS	ES	SE	CH	TR	UK	All EUR	USA	
Citrobacter freundii			2		2	3				2		19		2				2					32	137	286
Citrobacter koseri					19	3				3		2		2				3					32	69	218
Enterobacter aerogenes		15			2	15				2				15				2		15	15	15	96	349	499
Enterobacter asburiae																								3	3
Enterobacter cloacae					15	15	15			15			15		14	15		15			15	14	148	347	495
Escherichia coli					15	16	15			15			15	1	16	15		15			15	15	153	349	502
Klebsiella oxytoca					15	15	15			15			15		15	15		15			15	15	150	347	497
Klebsiella pneumoniae					15	15	15			15			14		15	14		14			15	15		35	497
Morganella morganii			15		15	2	1	1		15				19		1		25			1		95	67	216
Proteus mirabilis			15		15	15	15			15					15	15		15			15	15	150	258	408
Proteus vulgaris	1	1	9		15	2		1						15	15	1		2	15				77	6	209
Providencia rettgeri	2	1	1	1	4	7	3	1		1	1		3	4	1	4			3	1			38	13	51
Providencia stuartii	3	2	7		4	2	9	3	1	8		2		1	1	3	3	8					57	27	84
Serratia marcescens			15		15	15		15		15			15	15		15		15				15	150	347	497
Total	15	28	82	1	187	215	97	39	1	184	1	41	77	110	92	116	3	212	18	16	100	104	1739	2723	4462

AT, Austria; BE, Belgium; CZ, Czech Republic; DK, Denmark; FR, France; DE, Germany; EL, Greece; HU, Hungary; IE, Republic of Ireland; IT, Italy; LV, Latvia; NL, Netherlands; PL, Poland; PT, Portugal; RO, Romania; RU, Russia; RS, Republic of Serbia; ES, Spain; SE, Sweden; CH, Switzerland; TR, Turkey; UK, United Kingdom.

Figure 1. Cumulative percentage MIC distribution for eravacycline, tetracycline and tigecycline against *Enterobacteriaceae* from the USA (n=2,723)

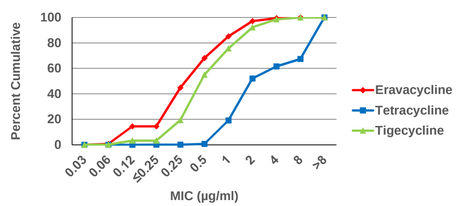


Figure 2. Cumulative percentage MIC distribution for eravacycline, tetracycline and tigecycline against *Enterobacteriaceae* from Europe (n=1,739)

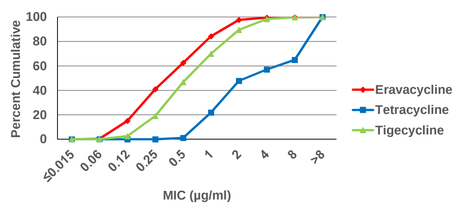


Table 2. Summary MIC data and susceptibility for all *Enterobacteriaceae* (n = 4,462)

Antibiotic	CLSI Breakpoints [S|I|R] (µg/ml)	Percentage			MIC (µg/ml)			
		S	I	R	MIC_{50}	MIC_{90}	Min	Max
Aztreonam	<=4 | 8 | >=16	84.7	1.3	14.1	<= 0.5	> 16	<= 0.5	> 16
Cefepime	<=8 | 16 | >=32	94.8	1.5	3.7	<= 0.25	2	<= 0.25	> 16
Ceftazidime	<=4 | 8 | >=16	85.3	1.1	13.5	<= 0.5	> 16	<= 0.5	> 16
Ceftriaxone	<=1 | 2 | >=4	80.3	2.0	17.7	<= 0.5	32	<= 0.5	> 32
Colistin	No Breakpoints Defined	-	-	-	1	> 4	<= 0.12	> 4
Eravacycline	No Breakpoints Defined	-	-	-	0.5	2	0.06	16
Gentamicin	<=4 | 8 | >=16	91.5	1.0	7.5	0.5	4	<= 0.25	> 8
Imipenem	<=1 | 2 | >=4	72.0	16.8	11.3	0.5	4	<= 0.25	> 8
Levofloxacin	<=2 | 4 | >=8	86.8	1.9	11.3	<= 0.25	> 4	<= 0.25	> 4
Pip/Taz	<=16/4 | 32/4-64/4 | >=128/4	87.4	9.0	3.6	2	32	<= 0.5	> 64
Tetracycline	<=4 | 8 | >=16	59.8	6.6	33.6	2	> 8	<= 0.25	> 8
Tigecycline	<=2 | 4 | >=8 *	91.1	7.3	1.6	0.5	2	<= 0.015	32

*, FDA breakpoints were used for tigecycline; S, I, R, percent of isolates susceptible, intermediate or resistant, respectively; Pip/Taz, piperacillin/tazobactam

Table 3. Summary MIC data and susceptibility for *Enterobacteriaceae* from the USA (n = 2,723)

Antibiotic	CLSI Breakpoints [S|I|R] (µg/ml)	Percentage			MIC (µg/ml)			
		S	I	R	MIC_{50}	MIC_{90}	Min	Max
Aztreonam	<=4 | 8 | >=16	81.9	1.6	16.5	<= 0.5	> 16	<= 0.5	> 16
Cefepime	<=8 | 16 | >=32	91.8	2.0	6.2	<= 0.25	4	<= 0.25	> 16
Ceftazidime	<=4 | 8 | >=16	82.4	1.3	16.4	<= 0.5	> 16	<= 0.5	> 16
Ceftriaxone	<=1 | 2 | >=4	76.5	2.1	21.4	<= 0.5	> 32	<= 0.5	> 32
Colistin	No Breakpoints Defined	-	-	-	1	> 4	<= 0.12	> 4
Eravacycline	No Breakpoints Defined	-	-	-	0.5	2	0.06	16
Gentamicin	<=4 | 8 | >=16	89.2	0.9	9.9	1	8	<= 0.25	> 8
Imipenem	<=1 | 2 | >=4	63.5	20.2	16.3	1	4	<= 0.25	> 8
Levofloxacin	<=2 | 4 | >=8	86.6	2.1	11.3	<= 0.25	> 4	<= 0.25	> 4
Pip/Taz	<=16/4 | 32/4-64/4 | >=128/4	86.5	8.8	4.7	2	32	<= 0.5	> 64
Tetracycline	<=4 | 8 | >=16	57.1	7.8	35.1	4	> 8	0.5	> 8
Tigecycline	<=2 | 4 | >=8 *	89.5	8.9	1.6	1	4	<= 0.015	32

*, FDA breakpoints were used for tigecycline; S, I, R, percent of isolates susceptible, intermediate or resistant, respectively; Pip/Taz, piperacillin/tazobactam

Table 4. Summary MIC data and susceptibility for *Enterobacteriaceae* from Europe (n = 1,739)

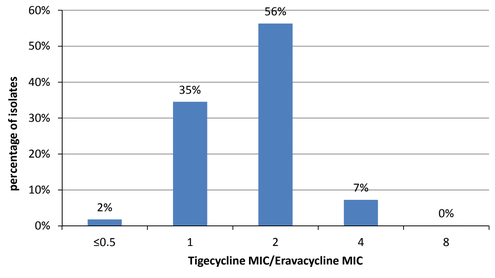
Antibiotic	CLSI Breakpoints [S|I|R] (µg/ml)	Percentage			MIC (µg/ml)			
		S	I	R	MIC_{50}	MIC_{90}	Min	Max
Aztreonam	<=4 | 8 | >=16	86.5	1.1	12.5	<= 0.5	> 16	<= 0.5	> 16
Cefepime	<=8 | 16 | >=32	96.7	1.1	2.2	<= 0.25	1	<= 0.25	> 16
Ceftazidime	<=4 | 8 | >=16	87.2	1.1	11.7	<= 0.5	> 16	<= 0.5	> 16
Ceftriaxone	<=1 | 2 | >=4	82.7	1.9	15.4	<= 0.5	32	<= 0.5	> 32
Colistin	No Breakpoints Defined	-	-	-	1	> 4	<= 0.12	> 4
Eravacycline	No Breakpoints Defined	-	-	-	0.5	2	0.06	8
Gentamicin	<=4 | 8 | >=16	93.0	1.0	6.0	0.5	2	<= 0.25	> 8
Imipenem	<=1 | 2 | >=4	77.3	14.6	8.1	0.5	2	<= 0.25	> 8
Levofloxacin	<=2 | 4 | >=8	87.0	1.8	11.3	<= 0.25	> 4	<= 0.25	> 4
Pip/Taz	<=16/4 | 32/4-64/4 | >=128/4	88.0	9.1	2.9	2	32	<= 0.5	> 64
Tetracycline	<=4 | 8 | >=16	61.6	5.9	32.6	2	> 8	<= 0.25	> 8
Tigecycline	<=2 | 4 | >=8 *	92.2	6.3	1.5	0.5	2	0.03	16

*, FDA breakpoints were used for tigecycline; S, I, R, percent of isolates susceptible, intermediate or resistant, respectively; Pip/Taz, piperacillin/tazobactam

Table 5. Summary MIC data for eravacycline against individual species of *Enterobacteriaceae* from Europe and the USA

Organism	Europe			USA		
	N	MIC_{50}	MIC_{90}	N	MIC_{50}	MIC_{90}
Citrobacter freundii	149	0.25	0.5	137	0.25	0.5
Citrobacter koseri	149	0.25	0.25	69	0.25	0.25
Enterobacter aerogenes	150	0.5	0.5	349	0.5	1
Enterobacter cloacae	148	0.5	1	347	0.5	1
Escherichia coli	153	0.12	0.25	349	0.12	0.25
Klebsiella oxytoca	150	0.25	0.25	347	0.25	0.5
Klebsiella pneumoniae	147	0.5	1	350	0.5	1
Morganella morganii	149	1	2	67	2	4
Proteus mirabilis	150	2	2	258	1	2
Proteus vulgaris	149	1	1	60	1	1
Providencia rettgeri	38	2	2	13	2	2
Providencia stuartii	57	1	4	27	1	4
Serratia marcescens	150	1	2	347	1	2

Figure 3: Comparison between tigecycline MIC and eravacycline MIC (all isolates)



- **A breakdown of the 4,462 *Enterobacteriaceae* collected by country of origin is shown in Table 1.**
- **Summary susceptibility and MIC data for eravacycline and comparators against all isolates combined and those from Europe and the USA are shown in Tables 2 to 4.**
- **A comparison of the activity of eravacycline against specific members of the *Enterobacteriaceae* from Europe and the USA are shown in Table 5.**
- **Eravacycline, tigecycline and tetracycline MIC distributions for isolates from the USA and Europe are shown in Figures 1 and 2.**
- **A direct comparison of tigecycline versus eravacycline MIC is shown in Figure 3.**

Conclusions

- Against a total of 4,462 *Enterobacteriaceae* clinical isolates, eravacycline exhibited the lowest MIC_{90} of 2 µg/ml (equal to cefepime and tigecycline).
- Eravacycline had a lower MIC distribution than tetracycline or tigecycline, with 64% of isolates having an eravacycline MIC ≥2-fold lower than tigecycline.
- Eravacycline activity was similar against isolates from the USA and Europe.
- Data from the recently completed Phase 3 trials will be used in determining the clinical breakpoints.
- Eravacycline exhibited excellent activity against the majority of isolates and shows promise for the treatment of infections caused by *Enterobacteriaceae*.

References

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