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Assessment of Eravacycline Against Non-fermenting Gram-Negative Clinical Isolates Isolated in 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 non-fermenters.

Methods: A total of 499 *Acinetobacter baumannii*, 499 *Pseudomonas aeruginosa* and 130 *Stenotrophomonas maltophilia* clinical isolates (collected in 2013-2014) were tested. MICs were determined by CLSI broth microdilution methodology. Susceptibility was assessed using CLSI breakpoints.

Results: Results are shown in the following Table:

	A. baumannii		*P. aeruginosa*		*S. maltophilia*	
Antibiotic	%S	MIC_{90}*	%S	MIC_{90}*	%S	MIC_{90}*
Eravacycline	NB	1	NB	16	NB	1
Tetracycline	27.3	> 8	NB	> 8	NB	>8
Tigecycline	NB	4	NB	32	NB	2
Aztreonam	NB	> 16	47.9	> 16	NB	>16
Cefepime	30.1	> 16	81.2	16	NB	>16
Ceftazidime	27.7	> 16	81.6	> 16	35.4	>16
Ceftriaxone	14.8	> 32	NB	> 32	NB	>32
Colistin	93.8	2	95.6	2	NB	>4
Gentamicin	32.9	> 8	84.4	> 8	NB	>8
Imipenem	37.3	> 8	61.5	> 8	NB	>8
Levofloxacin	21.8	> 4	67.3	> 4	3.1	4
Piperacillin/tazobactam	25.5	> 64	68.9	> 64	NB	>64

%S, percent susceptible; NB, no breakpoint. *MIC_{90} in µg/ml

Conclusions: Eravacycline was the most active agent against *A. baumannii* or *S. maltophilia* having a 4- or 2-fold lower MIC_{90} than tigecycline, respectively, and a >8-fold lower MIC_{90} than tetracycline. The MIC_{90} against the *P. aeruginosa* isolates was high for all compounds except colistin; the eravacycline MIC_{90} was 16 µg/ml against these predominantly MDR isolates. Eravacycline shows promising activity, especially against *A. baumannii* and *S. maltophilia*. 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 non-fermenting Gram-negative bacteria from both the USA and Europe.

Methods

A total of 1,128 isolates comprising 499 *Acinetobacter baumannii*, 499 *Pseudomonas aeruginosa* and 130 *Stenotrophomonas maltophilia* clinical isolates (collected in 2013-2014) were tested. A breakdown of infection type is shown in Figure 1.

Minimum inhibitory concentration (MIC) endpoints were determined by broth microdilution according to CLSI guidelines (1). Panels were prepared at IHMA using cation-adjusted Mueller-Hinton broth (CAMHB).

Quality control testing was performed each day of testing as specified by the CLSI using *Escherichia coli* ATCC 25922 and *Pseudomonas aeruginosa* ATCC 27853.

Antibiotic susceptibility was determined using CLSI 2015 breakpoints (2). FDA breakpoints were used for tigecycline (3).

Results

Table 1. Summary MIC data and susceptibility for all *A. baumannii* (n = 499)

Antibiotic	CLSI Breakpoints [S||R] (µg/ml)	Percentage			MIC (µg/ml)			
		S	I	R	MIC_{50}	MIC_{90}	Min	Max
Aztreonam	No Breakpoints Defined	-	-	-	> 16	> 16	<= 0.5	> 16
Cefepime	<=8 | 16 | >=32	30.1	21.0	48.9	16	> 16	<= 0.25	> 16
Ceftazidime	<=8 | 16 | >=32	27.7	4.0	68.3	> 16	> 16	<= 0.5	> 16
Ceftriaxone	<=8 | 16-32 | >=64	14.8	13.6	71.5	> 32	> 32	<= 0.5	> 32
Colistin	<=2 | -- | >=4	93.8	0.0	6.2	1	2	0.25	> 4
Eravacycline	**No Breakpoints Defined**	**-**	**-**	**-**	**0.5**	**1**	**0.03**	**4**
Gentamicin	<=4 | 8 | >=16	32.9	6.6	60.5	> 8	> 8	0.5	> 8
Imipenem	<=2 | 4 | >=8	37.3	1.2	61.5	> 8	> 8	<= 0.25	> 8
Levofloxacin	<=2 | 4 | >=8	21.8	3.6	74.6	> 4	> 4	<= 0.25	> 4
Pip/Taz	<=16/4 | 32/4-64/4 | >=128/4	25.5	5.0	69.5	> 64	> 64	<= 0.5	> 64
Tetracycline	<=4 | 8 | >=16	27.3	9.0	63.7	> 8	> 8	<= 0.25	> 8
Tigecycline	No Breakpoints Defined	-	-	-	1	4	0.06	8

S, I, R, percent of isolates susceptible, intermediate or resistant, respectively; Pip/Taz, piperacillin/tazobactam

Table 2. Summary MIC data and susceptibility for all *P. aeruginosa* (n = 499)

Antibiotic	CLSI Breakpoints [S||R] (µg/ml)	Percentage			MIC (µg/ml)			
		S	I	R	MIC_{50}	MIC_{90}	Min	Max
Aztreonam	No Breakpoints Defined	47.9	21.6	30.5	16	> 16	<= 0.5	> 16
Cefepime	<=8 | 16 | >=32	81.2	9.8	9.0	4	16	0.5	> 16
Ceftazidime	<=8 | 16 | >=32	81.6	4.8	13.6	2	> 16	<= 0.5	> 16
Ceftriaxone	<=8 | 16-32 | >=64	-	-	-	> 32	> 32	2	> 32
Colistin	<=2 | -- | >=4	95.6	3.8	0.6	2	2	0.5	> 4
Eravacycline	**No Breakpoints Defined**	**-**	**-**	**-**	**8**	**16**	**0.5**	**32**
Gentamicin	<=4 | 8 | >=16	84.4	4.4	11.2	2	> 8	<= 0.25	> 8
Imipenem	<=2 | 4 | >=8	61.5	10.4	28.1	2	> 8	<= 0.25	> 8
Levofloxacin	<=2 | 4 | >=8	67.3	5.2	27.5	1	> 4	<= 0.25	> 4
Pip/Taz	<=16/4 | 32/4-64/4 | >=128/4	68.9	16.0	15.0	8	> 64	<= 0.5	> 64
Tetracycline	<=4 | 8 | >=16	-	-	-	> 8	> 8	4	> 8
Tigecycline	No Breakpoints Defined	-	-	-	16	32	1	> 32

S, I, R, percent of isolates susceptible, intermediate or resistant, respectively; Pip/Taz, piperacillin/tazobactam

Table 3. Summary MIC data and susceptibility for all *S. maltophilia* (n = 130)

Antibiotic	CLSI Breakpoints [S||R] (µg/ml)	Percentage			MIC (µg/ml)			
		S	I	R	MIC_{50}	MIC_{90}	Min	Max
Aztreonam	No Breakpoints Defined	-	-	-	> 16	> 16	1	> 16
Cefepime	No Breakpoints Defined	-	-	-	> 16	> 16	0.5	> 16
Ceftazidime	<=8 | 16 | >=32	56.2	8.5	35.4	8	> 16	<= 0.5	> 16
Ceftriaxone	No Breakpoints Defined	-	-	-	> 32	> 32	1	> 32
Colistin (+ tween)	No Breakpoints Defined	-	-	-	<= 0.06	0.5	<= 0.06	> 4
Colistin	No Breakpoints Defined	-	-	-	1	> 4	<= 0.12	> 4
Eravacycline	**No Breakpoints Defined**	**-**	**-**	**-**	**0.5**	**1**	**0.03**	**8**
Gentamicin	No Breakpoints Defined	-	-	-	> 8	> 8	<= 0.25	> 8
Imipenem	No Breakpoints Defined	-	-	-	> 8	> 8	4	> 8
Levofloxacin	<=2 | 4 | >=8	83.1	13.9	3.1	1	4	<= 0.25	> 4
Pip/Taz	No Breakpoints Defined	-	-	-	64	> 64	2	> 64
Tetracycline	No Breakpoints Defined	-	-	-	> 8	> 8	1	> 8
Tigecycline	No Breakpoints Defined	-	-	-	0.5	2	0.06	8

S, I, R, percent of isolates susceptible, intermediate or resistant, respectively; Pip/Taz, piperacillin/tazobactam

- Tables 1 to 3 show summary MIC and susceptibility data for eravacycline and comparators against *A. baumannii*, *P. aeruginosa* and *S. maltophilia*, respectively.
- Cumulative percentage MIC distribution data for eravacycline and tigecycline are shown in Figures 2 to 4.
- A direct comparison of tigecycline versus eravacycline MICs against all combined non-fermenting Gram-negative bacteria is shown in Figure 5.

Figure 1. Origin of 1,128 non-fermenting Gram-negative isolates by infection source

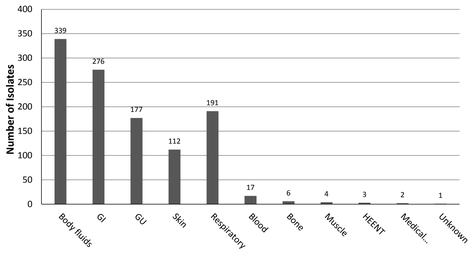


Figure 2. Cumulative percentage MIC distribution for eravacycline and tigecycline against all *A. baumannii* (n=499)

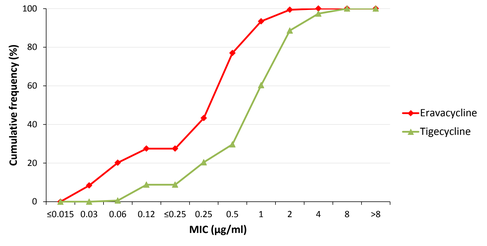


Figure 3. Cumulative percentage MIC distribution for eravacycline and tigecycline against all *P. aeruginosa* (n=499)

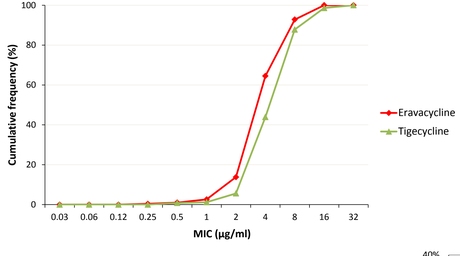


Figure 4. Cumulative percentage MIC distribution for eravacycline and tigecycline against all *S. maltophilia* (n=130)

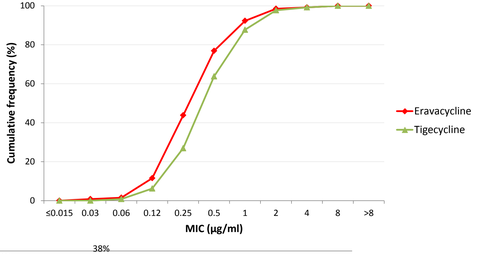
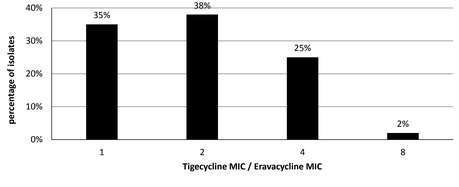


Figure 5. Comparison between tigecycline MIC and eravacycline MIC against all combined non-fermenting Gram-negative bacteria



Conclusions

- Eravacycline was the most active agent against *A. baumannii* or *S. maltophilia* having a 4- or 2-fold lower MIC_{90} than tigecycline, respectively, and a >8-fold lower MIC_{90} than tetracycline. The MIC_{90} against the *P. aeruginosa* isolates was high for all compounds except colistin; the eravacycline MIC_{90} was 16 µg/ml against these predominantly MDR isolates.
- All strains taken together, eravacycline had a lower MIC distributions than tetracycline or tigecycline, with 65% of isolates having a eravacycline MIC 2-fold or lower than tigecycline.
- Data from the recently completed Phase 3 trials will be used in determining the clinical breakpoints.
- Eravacycline exhibited excellent activity against many isolates and may show promise for the treatment of infections caused by non-fermenting Gram-negative bacteria.

References

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3. http://www.accessdata.fda.gov/drugsatfda_docs/label/2010/021821s021lbl.pdf

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