Presentation 566
Monday

Eravacycline is Active Against MDR, Cephalosporin- and Carbapenem-Resistant *Enterobacteriaceae* and *Acinetobacter baumannii*

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Abstract

Background: Eravacycline (ERV) is a novel, fully synthetic fluorocycline antibiotic of the tetracycline class being developed for the treatment of serious infections, including those caused by MDR pathogens. ERV was tested *in vitro* against Gram-negative pathogens of concern, including 3rd/4th generation cephalosporin-resistant (CEPH-R) and carbapenem-resistant (CP-R) *Enterobacteriaceae*, and CP-R and MDR *Acinetobacter baumannii*.

Methods. MIC assays were performed as per CLSI methodology and data for ERV was analyzed across multiple non-clinical and recent surveillance studies using a composite database housed at International Health Management Associates (IHMA). The IHMA Surveillance Data Link Network (SDLN) webtool was used to analyze isolates by resistance phenotypes, including MDR (resistant to ≥3 antibiotic classes), as per 2015 CLSI criteria. A subset of cephalosporin and/or carbapenem resistant isolates were screened using published PCR conditions for narrow- and extended-spectrum β-lactamases and carbapenemases.

Results. For most pathogens, ERV MIC$_{50/90}$ values increased ≤2-fold across resistant subclasses, indicating that ERV had *in vitro* potency against enterobacterial pathogens which are resistant to other antibacterials, including 3rd/4th generation cephalosporins and carbapenems, and MDR organisms. ERV had an overall MIC$_{50/90}$ of 0.5/2 µg/mL for a subset of 416 molecularly characterized CP-R *Enterobacteriaceae* which included 255 isolates positive for bla_{KPC} and 106 isolates positive for bla_{IMP}, bla_{VIM} or bla_{NDM} metallo-β-lactamase genes. The MIC$_{50/90}$ was 1/2 µg/mL for a subset of 220 CEPH-R, CP-R *Enterobacteriaceae*. The ERV MIC$_{50/90}$ for CP-R *A. baumannii* containing bla_{OXA} (n=94) was 0.5/1 µg/mL, and MIC values for strains with bla_{NDM} (n=5) and bla_{KPC} (n=1) were 0.12-0.25 µg/mL and 0.5 µg/mL, respectively.

Conclusions. ERV is active against difficult-to-treat CEPH-R, CP-R and MDR Gram-negative pathogens.

Introduction

Eravacycline is a novel, fully synthetic fluorocycline antibiotic of the tetracycline class that is being developed for the treatment of cIAI and cUTI, including pyelonephritis.

The antimicrobial spectrum of eravacycline activity includes clinically relevant:

- ESBL-producing *Enterobacteriaceae*
- Carbapenem-resistant (CRE) and multidrug-resistant (MDR) *Enterobacteriaceae*
- Carbapenem-resistant (CRAB) and MDR *Acinetobacter baumannii*
- Vancomycin-resistant enterococcus (VRE)
- Methicillin-resistant *Staphylococcus aureus* (MRSA)
- Streptococci
- Anaerobes such as *Bacteroides fragilis*.

The *in vitro* activity of eravacycline was assessed in multiple surveillance studies of isolates from the United States (US), the European Union (EU) and Canada in the past 2-3 years as well as in additional specialty *in vitro* studies.

Methods

The *in vitro* antibacterial activity of eravacycline was analyzed across multiple outsourced nonclinical and recent surveillance studies using a composite database assembled and housed at International Health Management Associates, Inc. (IHMA). The proprietary IHMA Surveillance Data Link Network (SDLN) webtool was used to analyze isolates by antibiotic resistance phenotypes, including MDR, according to the latest Clinical and Laboratory Standards Institute (CLSI) interpretive guidelines [1], and the eravacycline activity against large phenotypic subsets was determined. Activity of eravacycline against a subset of molecularly characterized, carbapenem-resistant *Enterobacteriaceae* and *A. baumannii* isolates identified as having specific β-lactamases and/or carbapenemase was analyzed by compiling susceptibility data across studies for eravacycline and comparators. Table 1 contains a brief description of the studies used in these analyses:

Table 1. Eravacycline Nonclinical and Surveillance Microbiology Studies Used in Analysis

Study	Year	Description	Ref
IHMA 2300	2013	A surveillance study performed at IHMA evaluated the activities of eravacycline and comparators against a recent (2013-2014) global collection of 9,551 clinical isolates including Enterobacteriaceae (n=4,462), Gram-negative non-fermenters (n=1,128), Gram-positive bacteria (n=3,467) and respiratory Gram-negative bacteria (n=494)	[2, 3]
CANWARD 2014	2015	A surveillance study performed by the Canadian Antimicrobial Resistance Alliance characterized the activities of eravacycline and comparators against pathogens isolated from Canadian hospitalized patients (13 sentinel hospital sites) including isolates from respiratory, skin/skin structure, urinary and bacteremic infections (n=2,637 isolates tested to date)	[4]
IHMA 2038	2013	In a disk diffusion vs. broth microdilution study performed at IHMA, eravacycline and comparators were tested against 1,440 clinical isolates including Enterobacteriaceae (n=607), non-fermenters (n=175), Gram-positive (n=579) and respiratory Gram-negative bacteria (n=79)	[5]
IHMA 2483	2015	The activity of eravacycline and comparators was determined against organisms collected during 2013-2014, with a focus on isolates with specific antibiotic resistance phenotypes, including multidrug resistance. This study surveyed 491 Enterobacteriaceae, 92 *P. aeruginosa*, 35 *B. fragilis*, and 97 *S. aureus*	[6]
Livermore Study MICRO15-7	2015	A study by David Livermore, et al. assessed the activity of eravacycline and comparators against molecularly-characterized carbapenems resistant and tigecycline non-susceptible Enterobacteriaceae and *Acinetobacter* spp. (n=369).	[7]
Bush Study MICRO15-10	2015	A study by Karen Bush's laboratory assessed the activity of eravacycline and comparators against molecularly characterized β lactamase producing carbapenem-resistant Enterobacteriaceae (n=110).	Zhang et al., ASM Microbe 2016 poster No. MO-550
Abdallah, et al.	2015	A study by David Landman's laboratory evaluated eravacycline and comparators against over 4,000 Gram-negative pathogens from New York City hospitals including *E. coli* (n=2,866), *K. pneumoniae* (n=944), *Enterobacter aerogenes* (n=90), *Enterobacter cloacae* (n=124) and *A. baumannii* (n=158).	[8]
Johnson Study	2015	In a study by the Johnson laboratory, the activity of eravacycline and comparators was evaluated against E. coli clinical isolates (n=472) from U.S. Veterans (2011) in relation to co-resistance phenotype and sequence type 131 genotype.	[9]
Tetraphase MICRO 10-13	2010	Eravacycline and comparators were tested at Tetraphase against panels of drug-resistant Enterobacteriaceae, including molecularly characterized isolates of *E. coli* (n=35), *Klebsiella oxytoca* (n=11), and *K. pneumoniae* (n=55) confirmed to possess ESBL genes	[10]
Eurofins 500951	2010	The activity profile of eravacycline and comparators was determined against 490 clinical isolates, including molecularly characterized *E. coli* (n=37) and *K. pneumoniae* (n=24), other Enterobacteriaceae (n=244), non-fermenters (n=58) and Gram-positive (n=127) isolates	[10]
Eurofins 100851	2011	The activity of eravacycline and comparators was determined against Enterobacteriaceae (n=200) and respiratory Gram-negative isolates (n=100)	[10]
Micromyx 03-10-2009-TetraPhase5	2009	The activity of eravacycline and comparators was evaluated against a set of 21 *A. baumannii*	[10]
Micromyx 05-12-2009-TetraPhase8	2009	The activity of eravacycline and comparators was evaluated by broth microdilution against a set of 1,147 clinical isolates including 317 Enterobacteriaceae	[10]

Results

Table 2. Eravacycline MIC Distributions (µg/mL) by Enterobacterial Species and Antibiotic Resistance Phenotype

Organism Phenotype	N	MIC (µg/mL) ≤0.015	0.03	0.06	0.12	0.25	0.5	1	2	4	8	16	MIC$_{50}$	MIC$_{90}$
Citrobacter freundii	**444**			**3**	**94**	**236**	**71**	**29**	**9**	**1**	**1**		**0.25**	**0.5**
CP-R	19					5	1	9	4				1	2
CEPH-R	159			1	23	80	35	14	5		1		0.25	1
MDR	80			1	8	35	18	12	5		1		0.25	1
AG-R	32			1	3	11	4	9	4				0.5	2
ATM-R	106			1	17	60	20	5	2		1		0.25	0.5
FQ-R	35				3	6	12	10	4				0.5	2
TET-R	52			1	7	20	13	7	3	1			0.25	1
TGC-R	1								1				NA	NA
TZP-R	70				8	31	16	10	4		1		0.25	1
Enterobacter aerogenes	**675**				**14**	**336**	**254**	**39**	**20**	**8**	**4**		**0.25**	**1**
CP-R	35					10	11	5	6	1	2		0.5	2
CEPH-R	212				3	89	80	19	14	6	1		0.5	1
MDR	69				1	14	21	13	11	6	3		0.5	4
AG-R	16				1	4	7	2	1	1			0.5	2
ATM-R	164				2	62	65	16	12	6	1		0.5	2
FQ-R	66				2	25	19	9	8	2	1		0.5	2
TET-R	52				2	6	9	7	16	8	4		2	4
TGC-R	5					2					3		NA	NA
TZP-R	30					8	12	6	2	2			0.5	2
Enterobacter cloacae	**1076**		**1**	**4**	**5**	**239**	**601**	**117**	**59**	**35**	**15**		**0.5**	**2**
CP-R	88					9	28	24	14	9	4		1	4
CEPH-R	479		1	4	3	86	225	80	48	24	8		0.5	2
MDR	271				1	38	87	58	48	27	12		1	4
AG-R	137					17	49	34	23	13	1		1	4
ATM-R	304				1	54	139	52	35	18	5		0.5	2
FQ-R	189					22	56	45	39	18	9		1	4
TET-R	188					20	57	25	39	32	15		1	4
TGC-R	24									11	13		8	8
TZP-R	193		1	1		27	60	46	38	17	3		1	4
Escherichia coli	**4901**	**1**	**12**	**524**	**2114**	**1538**	**587**	**108**	**10**	**7**			**0.12**	**0.5**
CP-R	111		1	8	31	45	14	8	2	2			0.25	1
CEPH-R	778		2	57	256	280	145	31	4	3			0.25	0.5
MDR	1081		2	56	280	413	252	66	6	6			0.25	0.5
AG-R	731		2	35	195	297	161	36	3	1			0.25	0.5
ATM-R	424		2	29	134	162	79	15	3				0.25	0.5
FQ-R	1621		3	106	475	618	324	81	7	7			0.25	0.5
TET-R	1641		4	74	524	617	334	74	10	4			0.25	0.5
TGC-R	1					1							NA	NA
TZP-R	179			21	64	63	21	8	2				0.25	0.5
Klebsiella oxytoca	**575**			**6**	**137**	**356**	**43**	**22**	**10**		**1**		**0.25**	**0.5**
CP-R	1				1								NA	NA
CEPH-R	62			2	4	37	8	7	4				0.25	1
MDR	33			1	2	18	4	4	4				0.25	2
AG-R	11			1	2	5	1	1	1				0.25	1
ATM-R	48			1	5	27	5	6	4				0.25	1
FQ-R	12					3	1	6	2				1	2
TET-R	28			1	5	10	3	5	3		1		0.25	2
TGC-R	1										1		NA	NA
TZP-R	20				1	12	2	2	3				0.25	2
Klebsiella pneumoniae	**2059**			**5**	**77**	**876**	**648**	**276**	**133**	**30**	**13**	**1**	**0.5**	**1**
CP-R	357				3	85	99	105	56	7	1	1	0.5	2
CEPH-R	614				10	191	180	151	67	12	3		0.5	2
MDR	639				9	186	183	165	75	13	7	1	0.5	2
AG-R	328				5	126	110	55	26	2	4		0.5	1
ATM-R	431				9	165	149	71	28	7	2		0.5	1
FQ-R	620				12	155	192	162	79	12	7	1	0.5	2
TET-R	436				13	126	117	85	62	24	8	1	0.5	2
TGC-R	28					3	4	5	1	7	7	1	4	8
TZP-R	263				4	84	107	49	16	1	2		0.5	1
Morganella morganii	**265**					**8**	**37**	**121**	**82**	**15**	**2**		**1**	**2**
CP-R	172					2	20	78	61	9	2		1	2
CEPH-R	37						1	13	17	6			2	4
MDR	47					1	2	13	20	10	1		2	4
AG-R	43					1	6	16	14	6			1	4
ATM-R	3								1	2			NA	NA
FQ-R	31						1	5	16	9			2	4
TET-R	124					2	17	49	44	11	1		1	2
TGC-R[a]	11								1	8	2		4	8
TZP-R	3									3			NA	NA
Proteus mirabilis	**647**					**8**	**78**	**268**	**250**	**42**	**1**		**1**	**2**
CP-R	266					1	18	98	120	29			2	4
CEPH-R	94					1	5	36	36	16			2	4
MDR	169					1	10	48	78	32			2	4
AG-R	123					1	7	40	57	18			2	4
ATM-R	15						1	7	5	2			1	4
FQ-R	154					2	7	55	69	21			2	4
TET-R	574					8	69	240	222	34	1		1	2
TGC-R[a]	88							11	48	29			2	4
TZP-R	6							1	3	2			NA	NA
Proteus vulgaris	**338**				**1**	**28**	**109**	**181**	**19**				**1**	**1**
CP-R	130					9	32	79	10				1	1
CEPH-R	51					6	15	26	4				1	1
MDR	27					3	5	14	5				1	2
AG-R	14					3	3	4	4				1	2
ATM-R	7						3	3	1				NA	NA
FQ-R	3							3					NA	NA
TET-R	120					8	41	59	12				1	1
TGC-R[a]	2							1	1				NA	NA
Providencia rettgeri	**71**					**1**	**4**	**18**	**37**	**10**	**1**		**2**	**4**
CP-R	10							3	2	4	1		2	4
CEPH-R	8					1		1	2	4			NA	NA
MDR	14					1		2	3	7	1		4	4
AG-R	10					1		2	3	3	1		2	4
ATM-R	4							1		3			NA	NA
FQ-R	23					1		5	8	8	1		2	4
TET-R	63					1	4	16	32	9	1		2	4
TGC-R[a]	2									1	1		NA	NA
Providencia stuartii	**262**				**2**	**5**	**46**	**99**	**75**	**25**	**5**	**5**	**1**	**4**
CP-R	49					1	2	17	21	4		4	2	4
CEPH-R	63					1	6	15	26	9	2	4	2	4
MDR	98					2	11	21	39	16	4	5	2	4
AG-R	83				1	1	10	25	28	11	2	5	2	4
ATM-R	19						1	2	9	3	1	3	2	16
FQ-R	152					2	23	46	52	20	4	5	2	4
TET-R	206					4	42	66	61	24	4	5	1	4
TGC-R[a]	25							1	6	9	4	5	4	16
TZP-R	18						1	4	7	1	1	4	2	16
Serratia marcescens	**673**					**2**	**70**	**351**	**214**	**30**	**6**		**1**	**2**
CP-R	21							7	9	4	1		2	4
CEPH-R	108					1	8	47	43	8	1		1	2
MDR	43						1	12	20	9	1		2	4
AG-R	19						1	7	8	3			2	4
ATM-R	24						2	11	6	4	1		1	4
FQ-R	30						3	7	15	5			2	4
TET-R	462					1	40	206	181	28	6		1	2
TGC-R	4								1	1	2		NA	NA
TZP-R	6							2	2	2			NA	NA

CP-R=carbapenem-resistant; CEPH-R=3rd/4th generation cephalosporin-resistant; MDR=multidrug-resistant as defined by resistance to≥3 classes of antibiotics; AG-R=aminoglycoside-resistant; ATM-R=aztreonam-resistant; FQR=fluoroquinolone-resistant; TET-R=tetracycline-resistant; TGC-R=tigecycline-resistant; TZP-R= piperacillin/tazobactam-resistant; resistance defined by CLSI [1]; FDA breakpoints were used for tigecycline; NA=not available.
[a]TGC-R=Tigecycline has decreased in vitro activity against *Morganella* spp., *Proteus* spp. and *Providencia* spp.

Table 3 *In Vitro* Activity of Eravacycline against Molecularly Characterized Carbapenem-resistant *Enterobacteriaceae*

Species/β-lactamase	Compound	MIC$_{50/90}$ (µg/mL)	Range (µg/mL)	N
Enterobacteriaceae				
Carbapenem-resistant[1]	eravacycline	0.5/2	(0.125-16)	416
	tigecycline	2/4	(0.125-16)	409
Metallo-β-lactamases (IMP, VIM, NDM)	eravacycline	0.5/4	(0.125-8)	106
	tigecycline	1/4	(0.125-8)	106
IMP	eravacycline	0.5/2	(0.125-2)	12
	tigecycline	0.5/4	(0.25-4)	12
NDM	eravacycline	0.5/4	(0.125-8)	59
	tigecycline	1/8	(0.125-8)	59
VIM	eravacycline	1/4	(0.25-8)	35
	tigecycline	1/4	(0.25-8)	35
KPC	eravacycline	1/2	(0.12-16)	255
	tigecycline	2/2	(0.25-16)	255
AmpC	eravacycline	NA	(0.5-2)	7
	tigecycline	NA	(1-4)	7
OXA	eravacycline	1/4	(0.25-8)	32
	tigecycline	2/4	(0.25-16)	32
Porin Loss	eravacycline	0.5/2	(0.125-4)	26
	tigecycline	1/4	(0.25-8)	26
***Citrobacter* spp.**				
VIM	eravacycline	NA	(0.5-0.5)	1
	tigecycline	NA	(1-1)	1
KPC	eravacycline	NA	(1-1)	2
	tigecycline	NA	(2-2)	2
OXA	eravacycline	NA	(4-4)	1
	tigecycline	NA	(8-8)	1
***Enterobacter* spp.**				
IMP	eravacycline	NA	(0.25-2)	2
	tigecycline	NA	(0.5-4)	2
VIM	eravacycline	1/8	(0.25-8)	10
	tigecycline	2/4	(0.5-8)	10
NDM	eravacycline	0.5/2	(0.25-4)	13
	tigecycline	1/4	(0.5-8)	13
KPC	eravacycline	0.5/8	(0.25-8)	15
	tigecycline	1/8	(0.25-8)	12
AmpC	eravacycline	NA	(0.5-2)	7
	tigecycline	NA	(1-4)	7
OXA	eravacycline	NA	(1-8)	5
	tigecycline	NA	(1-16)	5
Porin Loss	eravacycline	NA	(0.5-2)	5
	tigecycline	NA	(1-4)	5

NA=not available

Species/β-lactamase	Compound	MIC$_{50/90}$ (µg/mL)	Range (µg/mL)	N
E. coli				
NDM	eravacycline	0.13/0.25	(0.125-0.5)	11
	tigecycline	0.25/0.5	(0.125-0.5)	11
VIM	eravacycline	NA	(0.25-4)	6
	tigecycline	NA	(0.25-4)	6
KPC	eravacycline	1/4	(0.125-4)	12
	tigecycline	1/2	(0.25-4)	12
OXA	eravacycline	NA	(0.25-4)	8
	tigecycline	NA	(0.25-2)	8
Porin Loss	eravacycline	NA	(0.125-0.5)	7
	tigecycline	NA	(0.25-0.5)	7
K. pneumoniae				
IMP	eravacycline	NA	(0.25-2)	6
	tigecycline	NA	(0.5-4)	6
NDM	eravacycline	0.5/4	(0.25-8)	28
	tigecycline	1/8	(0.25-8)	28
VIM	eravacycline	1/2	(0.25-2)	18
	tigecycline	1/4	(0.5-4)	18
KPC	eravacycline	1/2	(0.12-16)	222
	tigecycline	2/2	(0.25-16)	222
OXA	eravacycline	1/2	(0.25-2)	15
	tigecycline	2/2	(1-4)	15
Porin Loss	eravacycline	1/4	(0.25-4)	14
	tigecycline	1/8	(0.25-8)	14
***Klebsiella* spp.**				
IMP	eravacycline	NA	(0.125-2)	4
	tigecycline	NA	(0.25-4)	4
KPC	eravacycline	NA	(0.5-1)	2
	tigecycline	NA	(0.25-1)	2
***Proteeae* spp.**				
NDM	eravacycline	NA	(4-8)	5
	tigecycline	NA	(4-8)	5
OXA	eravacycline	NA	(1-1)	1
	tigecycline	NA	(2-2)	1
S. marcescens				
NDM	eravacycline	NA	(1-4)	2
	tigecycline	NA	(2-4)	2
KPC	eravacycline	NA	(2-4)	5
	tigecycline	NA	(2-4)	5
OXA	eravacycline	NA	(1-4)	2
	tigecycline	NA	(1-4)	2

Table 4. Eravacycline MIC Distributions (µg/mL) for *A. baumannii* by Antibiotic Resistance Phenotype

Organism	N	MIC (µg/mL) ≤0.03	0.06	0.12	0.25	0.5	1	2	4	8	MIC$_{50}$	MIC$_{90}$
A. baumannii	**851**	**68**	**99**	**77**	**126**	**257**	**158**	**52**	**9**	**5**	**0.5**	**1**
CP-R	511		9	29	85	190	135	50	9	4	0.5	2
CEPH-R	514		11	31	99	207	120	41	3	2	0.5	1
MDR	574		10	35	102	225	144	46	8	4	0.5	2
AG-R	455	2	6	27	73	172	121	43	8	3	0.5	2
FQ-R	572	2	10	35	99	221	146	46	8	5	0.5	2
TET-R	519	1	9	22	72	218	138	49	6	4	0.5	2
TGC-R[a]	98					8	38	40	9		2	4
TZP-R	505		10	30	91	199	123	43	6	3	0.5	2

CP-R=carbapenem-resistant; CEPH-R=3rd/4th generation cephalosporin-resistant; MDR=multidrug-resistant as defined by resistance to ≥3 classes of antibiotics; AG-R=aminoglycoside-resistant; FQ-R=fluoroquinolone-resistant; TET-R=tetracycline-resistant; TGC-R=tigecycline-resistant; TZP-R= piperacillin/tazobactam-resistant; resistance defined by CLSI [1].

Table 5. *In Vitro* Activity of Eravacycline against Molecularly Characterized Carbapenem-resistant *A. baumannii*

Species/β-lactamase	Compound	MIC$_{50/90}$ (µg/mL)	Range (µg/mL)	n
A. baumannii				
All OXA[1]	eravacycline	0.5/1	(0.0625-8)	94
	tigecycline	2/4	(0.25-4)	94
OXA-23	eravacycline	0.5/1	(0.12-8)	65
	tigecycline	2/>2	(0.5-4)	65
OXA-24	eravacycline	1/1	(0.5-2)	12
	tigecycline	2/4	(1-4)	12
OXA-40	eravacycline	1/1	(0.5-2)	10
	tigecycline	2/4	(1-4)	10
OXA-51	eravacycline	NA	(0.5-2)	8
	tigecycline	NA	(1-4)	8
OXA-58	eravacycline	1/1	(0.0625-1)	10
	tigecycline	2/2	(0.25-4)	10
NDM	eravacycline	NA	(0.125-0.25)	5
	tigecycline	NA	(0.5-1)	5
KPC	eravacycline	NA	(0.5-0.5)	1
	tigecycline	NA	(>2->2)	1

[1] some isolates contain more than one OXA-type enzyme

Conclusions

In vitro microbiology studies support eravacycline's potential to address unmet medical needs in the treatment of serious infections caused by Gram-negative pathogens of concern, including ESBL-*Enterobacteriaceae*, CRE, CRAB, and MDR *Acinetobacter*.

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