

In vitro activity of eravacycline and comparators against Enterobacteriaceae, including subgroups of strains with resistance to carbapenems or 3rd/4th generation cephalosporins, isolated from patients in Europe

Matteo Bassetti¹, Ian Morrissey², Trudy Grossman³, Katherine Luepke³, Patrick Scoble³, Joyce Sutcliffe³
¹Santa Maria Misericordia Hospital, Udine, Italy; ²IHMA Europe Sarl, Epalinges, Switzerland; ³Tetraphase Pharmaceuticals, Watertown, MA, USA

Introduction

Eravacycline is a novel, fully-synthetic fluorocycline antibiotic of the tetracycline class with broad-spectrum activity in development for the treatment of serious infections, including those caused by MDR pathogens. Eravacycline has been evaluated in phase 3 studies for the treatment of cIAI and for cUTI, including pyelonephritis.

The purpose of this study was to evaluate in vitro activity of eravacycline and comparators against Enterobacteriaceae, including isolates from patients in Europe resistant to carbapenems or 3rd/4th generation cephalosporins.

Methods

In this study, a total of 1739 clinical isolates were collected from 2013-2014, including MDR isolates, which were collected based on a target number for specific organisms with preference given to IAI and UTI.

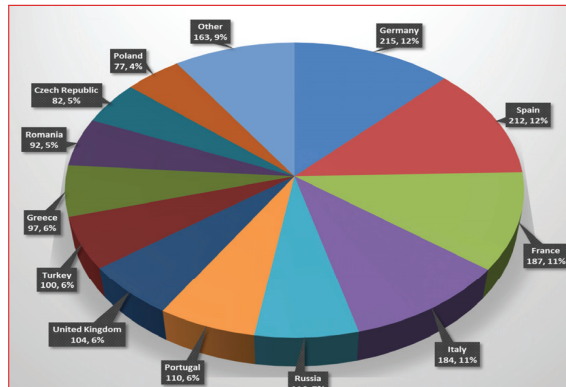
- Minimum inhibitory concentration (MIC) endpoints were determined by broth microdilution according to CLSI guidelines (1).
- Quality control testing was performed each day of testing as specified by the CLSI using *E. coli* ATCC 25922, *E. coli* ATCC 35218, and *P. aeruginosa* ATCC 27853.
- Antibiotic susceptibility was determined using EUCAST breakpoints (2).
- 3rd/4th GC-R was defined as resistance to any one of the following:
 - ceftriaxone, cefotaxime, ceftazidime, cefepime
- CR was defined as resistance to imipenem.

Results

The eravacycline MIC_{50/90} for all Enterobacteriaceae was 0.5/2 mg/L. The eravacycline MIC_{50/90} for 3rd/4th GC-R and CR isolates were 0.5/2 and 1/16 mg/L, respectively. The CR isolates MIC₉₀ of 16mg/L was largely driven by four *Providencia stuartii* isolates with MICs of 16mg/L.

- Summary of MIC_{50/90} for eravacycline, as well as cumulative MIC distribution for eravacycline against Enterobacteriaceae, including drug-resistant phenotypes, are shown in Table 1.
- The antimicrobial activity of eravacycline and comparator agents against Enterobacteriaceae isolates, including drug-resistant phenotypes, and MIC range results for eravacycline against Enterobacteriaceae are shown in Table 2.
- Country of origin for the clinical isolates is shown in Figure 1.
- Figure 2 shows the isolate counts by source of infection (N=1739).

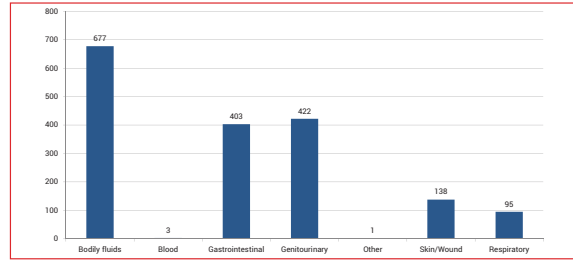
Figure 1. Country of Origin (N, %) for the 1739 Enterobacteriaceae isolates tested



UK, United Kingdom of Great Britain and Northern Ireland; Countries included as "Other" (Austria, Belgium, Denmark, Hungary, Republic of Ireland, Latvia, Netherlands, Serbia, Sweden, and Switzerland) had less than 41 isolates each.

Results (cont'd)

Figure 2. Isolate counts by source of infection (N=1739)



Bodily Fluids Sources: Abscess / Pus, Abdominal, Pericardial, Peritoneal, Thoracentesis, Tissue, and Ulcer

Table 1. Cumulative MIC distribution for eravacycline for Enterobacteriaceae, including drug resistant phenotypes (n>5)

Organism (No. Tested)	Number of isolates (cumulative) inhibited at eravacycline MIC (mg/L) of:							
	<0.03	0.03	0.06	0.12	0.25	0.5	1	>16
C. freundii (149)	31 (20.8)	27 (34.3)	14 (9.4)	5 (3.0)	0	0	0	0
C. freundii 3rd/4th GC-R (48)	13 (27)	27 (56.3)	7 (14.6)	2 (4.2)	0	0	0	0
C. koseri (149)	63 (42.3)	13 (9.3)	1 (0.7)	1 (0.7)	0	0	0	0
E. aerogenes (150)	3 (2)	64 (44.7)	24 (16.4)	7 (9.3)	1 (0.7)	0	0	0
E. aerogenes 3rd/4th GC-R (99)	21 (26.6)	30 (38.4)	19 (24.3)	7 (9.3)	1 (1.3)	0	0	0
E. cloacae (148)	1 (0.7)	20 (14.2)	12 (8.3)	11 (9.1)	6 (9.3)	6 (9.3)	1 (0.7)	0
E. cloacae 3rd/4th GC-R (60)	1 (1.6)	13 (22.2)	24 (40.7)	4 (9.5)	4 (9.5)	1 (0.0)	0	0
E. cloacae CR (8)	1 (12.5)	1 (12.5)	1 (12.5)	1 (12.5)	1 (12.5)	1 (12.5)	1 (12.5)	1 (12.5)
E. coli 3rd/4th GC-R (43)	7 (16.3)	30 (69.8)	7 (16.3)	1 (2.3)	0	0	0	0
E. coli 3rd/4th GC-R (13)	2 (15.4)	10 (76.9)	1 (7.7)	0	0	0	0	0
E. coli 3rd/4th GC-R (10)	2 (20)	10 (100)	0	0	0	0	0	0
E. coli CR (1)	1 (100)	0	0	0	0	0	0	0
E. coli 3rd/4th GC-R (11)	1 (9.1)	7 (63.6)	1 (9.1)	0	0	0	0	0
E. coli CR (1)	1 (100)	0	0	0	0	0	0	0
E. coli 3rd/4th GC-R (10)	1 (10)	4 (40)	4 (40)	1 (10)	0	0	0	0
E. coli CR (1)	1 (100)	0	0	0	0	0	0	0
E. coli 3rd/4th GC-R (10)	1 (10)	4 (40)	4 (40)	1 (10)	0	0	0	0
E. coli CR (1)	1 (100)	0	0	0	0	0	0	0
E. coli 3rd/4th GC-R (10)	1 (10)	4 (40)	4 (40)	1 (10)	0	0	0	0
E. coli CR (1)	1 (100)	0	0	0	0	0	0	0
E. coli 3rd/4th GC-R (10)	1 (10)	4 (40)	4 (40)	1 (10)	0	0	0	0
E. coli CR (1)	1 (100)	0	0	0	0	0	0	0
E. coli 3rd/4th GC-R (10)	1 (10)	4 (40)	4 (40)	1 (10)	0	0	0	0
E. coli CR (1)	1 (100)	0	0	0	0	0	0	0

Underscored = MIC₅₀; Red text = MIC₉₀; "NA" = MIC₅₀ or MIC₉₀ not applicable for species with isolates of N<10

Table 2. Antimicrobial activity of eravacycline and comparator agents against Enterobacteriaceae, including drug-resistant phenotypes

Organism/Antimicrobial Agent (No. Tested)	MIC ₅₀	MIC ₉₀	Range	% S / U / R ^a	
				EUCAST	CLSI
Enterobacteriaceae (1739)	0.05	0.5	<0.5-16	78.5/3	41/81
Aztreonam	≤0.5	>16	<0.5-16	80.8/2	5/37
Cefepime	≤0.5	>16	<0.5-16	81.2/2	5/37
Ceftriaxone	≤0.5	>16	<0.5-16	77.6/4	7/71.8
Colistin	0.05	0.5	<0.12-4	76.5/2	1/21.4
Eravacycline	0.5	2	0.06-16	82.4/5	4/40.4
Genitamicin	1	8	<0.25-8	84.3/4	0/0
Imipenem	0.5	2	<0.25-8	83.7/4	1/16
Levofloxacin	≤0.25	>4	<0.25-8	83.3/4	3/13.4
Piperacillin/tazobactam	1	8	<0.5-8	83.2/3	3/13.4
Tetracycline	4	4	0.5-8	-/-	-/-
Tigecycline	1	4	<0.015-32	70/19	5/16.5
Enterobacteriaceae 3rd/4th GC-R (387)	0.05	0.5	<0.5-16	82.4/3	17/38.8
Aztreonam	≤0.5	>16	<0.5-16	43/21.2	3/43.7
Cefepime	≤0.5	>16	<0.5-16	71.5/15	2/31.3
Ceftriaxone	≤0.5	>16	<0.5-16	14.2/36.1	2/53.2
Colistin	0.05	0.5	0.12-4	71.3	-/28.7
Eravacycline	0.5	2	0.06-16	81.5/13	3/13.4
Genitamicin	1	8	<0.25-8	81.2/3	0/0
Imipenem	0.5	2	<0.25-8	80.9/9	1/16
Levofloxacin	≤0.25	>4	<0.25-8	80.8/9	3/13.4
Piperacillin/tazobactam	1	8	<0.5-8	80.7/9	4/13.4
Tetracycline	4	4	0.5-8	-/-	-/-
Tigecycline	1	4	<0.015-32	70/19	5/16.5

Table 2. Antimicrobial activity of eravacycline and comparator agents against Enterobacteriaceae, including drug-resistant phenotypes (cont'd)

Organism/Antimicrobial Agent (No. Tested)	MIC ₅₀	MIC ₉₀	Range	% S / U / R ^a	
				EUCAST	CLSI
Enterobacteriaceae CR (28)	0.05	0.5	<0.5-16	14.3/3	0/21
Aztreonam	>16	>16	<0.5-16	3.6/3	0/21
Cefepime	>16	>16	<0.5-16	3.6/3	0/21
Ceftriaxone	>16	>16	<0.5-16	3.6/3	0/21
Colistin	>16	>16	<0.5-16	3.6/3	0/21
Eravacycline	0.5	2	0.06-16	100/0	0/0
Genitamicin	1	8	<0.25-8	100/0	0/0
Imipenem	0.5	2	<0.25-8	100/0	0/0
Levofloxacin	>4	>4	<0.25-8	100/0	0/0
Piperacillin/tazobactam	>4	>4	<0.25-8	100/0	0/0
Tetracycline	4	4	0.5-8	-/-	-/-
Tigecycline	2	16	0.32	42.9/25	2/21
Enterobacter spp. (296)	0.05	0.5	<0.5-16	80.5/2	41/71.1
Aztreonam	≤0.5	>16	<0.5-16	96/23	1/2
Cefepime	≤0.5	>16	<0.5-16	96/23	1/2
Ceftriaxone	≤0.5	>16	<0.5-16	81.9/30	7/71.8
Colistin	0.05	0.5	<0.12-4	88.7/17	0
Eravacycline	0.25	0.5	0.12	-/-	-/-
Genitamicin	0.5	2	<0.25-8	97.3/7	2
Imipenem	0.5	2	<0.25-8	98.7/3	2
Levofloxacin	≤0.25	2	<0.25-8	97.1/11	2
Piperacillin/tazobactam	1	8	<0.5-8	96.6/7	2
Tetracycline	2	4	0.5-8	-/-	-/-
Tigecycline	0.5	0.5	0.015-2	99.3/0	0
Enterobacter 3rd/4th GC-R (13)	0.05	0.5	<0.5-16	60.3/3	7/13
Aztreonam	≤0.5	>16	<0.5-16	46/23	0
Cefepime	≤0.5	>16	<0.5-16	46/23	0
Ceftriaxone	≤0.5	>16	<0.5-16	60/30	7/13
Colistin	0.05	0.5	<0.12-4	50/13	0
Eravacycline	0.5	0.5	0.25	-/-	-/-
Genitamicin	0.5	2	<0.25-8	90/2	0
Imipenem	0.5	2	<0.25-8	96.7/7	2
Levofloxacin	≤0.25	>4	<0.25-8	88/21	0
Piperacillin/tazobactam	2	16	<0.5-8	86.6/7	2
Tetracycline	1	4	0.5-8	-/-	-/-
Tigecycline	0.5	0.5	0.015-2	99.3/0	0
E. aerogenes (156)	0.05	0.5	<0.5-16	60.3/3	7/13
Aztreonam	≤0.5	>16	<0.5-16	46/23	0
Cefepime	≤0.5	>16	<0.5-16	46/23	0
Ceftriaxone	≤0.5	>16	<0.5-16	60/30	7/13
Colistin	0.05	0.5	<0.12-4	50/13	0
Eravacycline	0.5	0.5	0.25	-/-	-/-
Genitamicin	0.5	2	<0.25-8	90/2	0
Imipenem	0.5	2	<0.25-8	96.7/7	2
Levofloxacin	≤0.25	>4	<0.25-8	88/21	0
Piperacillin/tazobactam	2	16	<0.5-8	86.6/7	2
Tetracycline	1	4	0.5-8	-/-	-/-
Tigecycline	0.5	0.5	0.015-2	99.3/0	0
E. aerogenes 3rd/4th GC-R (99)	0.05	0.5	<0.5-16	56.3/2	4/40.5
Aztreonam	≤0.5	>16	<0.5-16	42.1/17	0
Cefepime	≤0.5	>16	<0.5-16	42.1/17	0
Ceftriaxone	≤0.5	>16	<0.5-16	56.3/2	4/40.5
Colistin	0.05	0.5	<0.12-4	46/23	0
Eravacycline	0.5	0.5	0.25	-/-	-/-
Genitamicin	0.5	2	<0.25-8	90/2	0
Imipenem	0.5	2	<0.25-8	96.7/7	2
Levofloxacin	≤0.25	>4	<0.25-8	88/21	0
Piperacillin/tazobactam	2	16	<0.5-8	86.6/7	2
Tetracycline	1	4	0.5-8	-/-	-/-
Tigecycline	0.5	0.5	0.015-2	99.3/0	0
E. coli CR (1)	0.5	0.5	0.25	-/-	-/-
Aztreonam	≤0.5	>16	<0.5-16	56.3/2	4/40.5
Cefepime	≤0.5	>16	<0.5-16	56.3/2	4/40.5
Ceftriaxone	≤0.5	>16	<0.5-16	60/30	7/13
Colistin	0.05	0.5	<0.12-4	50/13	0
Eravacycline	0.5	0.5	0.25	-/-	-/-
Genitamicin	0.5	2	<0.25-8	90/2	0
Imipenem	0.5	2	<0.25-8	96.7/7	2
Levofloxacin	≤0.25	>4	<0.25-8	88/21	0
Piperacillin/tazobactam	2	16	<0.5-8	86.6/7	2
Tetracycline	1	4	0.5-8	-/-	-/-
Tigecycline	0.5	0.5	0.015-2	99.3/0	0
E. coli 3rd/4th GC-R (43)	0.05	0.5	<0.5-16	56.3/2	4/40.5
Aztreonam	≤0.5	>16	<0.5-16	42.1/17	0
Cefepime	≤0.5	>16	<0.5-16	42.1/17	0
Ceftriaxone	≤0.5	>16	<0.5-16	60/30	7/13
Colistin	0.05	0.5	<0.12-4	46/23	0
Eravacycline	0.5	0.5	0.25	-/-	-/-
Genitamicin	0.5	2	<0.2		