FRIDAY - 604

Restoration of Sulbactam Activity by the Novel β-lactamase Inhibitor ETX2514 Against Recent Clinical Isolates of *Acinetobacter baumannii*, Including Extensively Drug-Resistant (XDR) Isolates Expressing OXA-237

S. McLeod[1], S. Moussa[1], M. Hackel[2], R. Badal[2], J. Mueller[1], R. Tommasi[1], and A. Miller[1]

[1]Entasis Therapeutics, Waltham, MA and [2]IHMA, International Health Management Associates, Schaumburg, IL USA

Entasis Therapeutics
1-781-810-0120
sarah.mcleod@entasistx.com

Abstract

Background

ETX2514 is a novel, diazabicyclooctenone β-lactamase inhibitor with broad-spectrum activity against class A, C and D serine β-lactamases. ETX2514 restores β-lactam activity against multidrug-resistant Gram-negative bacteria. ETX2514 combined with sulbactam is currently in clinical development for the treatment of *Acinetobacter baumannii* infections. *A. baumannii* can cause severe infections that are notoriously difficult to treat due to increasing resistance to antibacterial therapy. We sought to determine the relative potency of sulbactam-ETX2514 against recent, geographically diverse *A. baumannii* isolates.

Methods

848 *A. baumannii* isolates collected during 2016 from geographically diverse medical centers in the United States, Europe, Latin America, Middle East and the Asia-Pacific region were chosen for testing. In addition, 16 XDR *A. baumannii* expressing the class D β-lactamase OXA-237 from an outbreak that occurred in Oregon, USA, between 2012-2014 (Hujer *et al*., 2017, Antimicrob. Agents Chemother., 61: e00797-17) were tested. Susceptibility testing was performed according to CLSI guidelines, and data analysis was performed using CLSI breakpoint criteria.

Results

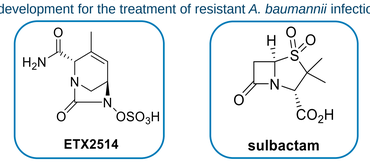
Sulbactam-ETX2514 was highly active against the collections of *A. baumannii* isolates. In surveillance of 848 global isolates from 2016, the addition of 4 mg/L ETX2514 decreased the sulbactam MIC_{90} from >32 to 2 mg/L. This level of potency was found to be consistent across regions, sources of infection and subsets of resistance phenotypes. Only ten isolates were found to have MICs ≥8 mg/L to sulbactam-ETX2514. Against a separate set of 16 XDR, OXA-237+ *A. baumannii* isolates from an outbreak in Oregon, sulbactam MIC values ranged from 8 to >64 mg/L while sulbactam-ETX2514 MIC values ranged from 2-8 mg/L, suggesting ETX2514 can inhibit the OXA-237 carbapenemase and that the combination of sulbactam and ETX2514 could be an effective treatment for infections caused by these XDR strains.

Conclusions

The combination of sulbactam and ETX2514 demonstrated potent antibacterial activity against recent, geographically diverse clinical isolates of *A. baumannii*, including XDR isolates from an outbreak in Oregon. These data support the continued development of ETX2514 in combination with sulbactam for the treatment of antibiotic-resistant *A. baumannii* infections.

Introduction

Sulbactam-ETX2514 is a β-lactam/β-lactamase inhibitor combination currently in clinical development for the treatment of resistant *A. baumannii* infections[1].



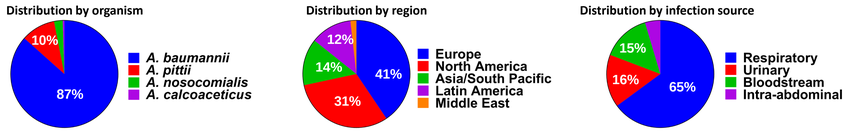
ETX2514 is a novel BLI from a series of diazabicyclooctenones with best-in-class broad spectrum activity against class A, C and D β-lactamases.

Methods

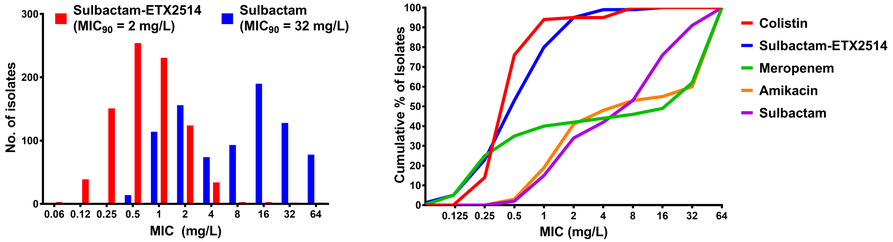
Broth microdilution susceptibility testing was conducted according to CLSI guidelines using cation-adjusted Mueller-Hinton broth[2]. Sulbactam-ETX2514 was tested by dilution of sulbactam in the presence of a fixed concentration of 4 mg/L ETX2514. Testing of the 848 global *A. baumannii* isolates was performed at IHMA laboratories. The 16 XDR, OXA-237+ *A. baumannii*[3] were a kind gift from Dr. Robert Bonomo and were tested at Entasis for sulbactam-ETX2514 susceptibility.

2016 Sulbactam-ETX2514 Global Surveillance Study Design

848 *Acinetobacter baumannii calcoaceticus* complex isolates
(Collected in global surveillance program of 2016 by IHMA)



ETX2514 Restores Sulbactam Activity Against Geographically Diverse *A. baumannii* from 2016



		Number (cumulative %) of isolates inhibited at MIC (mg/L)											
Antimicrobial	**%S***	**≤0.03**	**0.06**	**0.125**	**0.25**	**0.5**	**1**	**2**	**4**	**8**	**16**	**32**	**≥64**
Sulbactam	NA				1	14	114	156	74	93	190	**128**	78
		0%	0%	0%	0%	2%	15%	34%	42%	53%	76%	**91%**	100%
Sulbactam-ETX2514	NA	2	3	39	151	254	231	**124**	34	3	3	2	2
		0%	1%	5%	23%	53%	80%	**95%**	99%	99%	100%	100%	100%
Amikacin	55					26	137	182	63	38	21	39	**342†**
		0%	0%	0%	0%	3%	19%	41%	48%	53%	55%	60%	**100%**
Cefepime	38			1	1	10	59	136	79	36	**526†**		
		0%	0%	0%	0%	1%	8%	24%	34%	38%	**100%**	100%	100%
Ciprofloxacin	36			123	139	35	11	4	**536†**				
		0%	0%	15%	31%	35%	36%	37%	**100%**	100%	100%	100%	100%
Colistin	95				120	523	**153**	8	1	43			
		0%	0%	0%	14%	76%	**94%**	95%	95%	100%	100%	100%	100%
Imipenem	43		12	101	209	9	27	10	5	19	39	121	**296†**
		0%	1%	13%	38%	39%	42%	43%	44%	46%	51%	65%	**100%**
Meropenem	42		1	43	171	82	43	19	12	20	26	109	**322†**
		0%	0%	5%	25%	35%	40%	42%	44%	46%	49%	62%	**100%**
Minocycline	80			293	80	81	72	57	99	**85**	81		
		0%	0%	35%	44%	54%	62%	69%	80%	**90%**	100%	100%	100%
Tigecycline	NA	3	67	144	125	143	270	**78**	14	2		2	
		0%	8%	25%	40%	57%	89%	**98%**	100%	100%	100%	100%	100%

*Based on 2018 CLSI breakpoint criteria[4]. NA = not available. MIC_{90}s are highlighted with blue squares. †Top concentration tested so MIC_{90} could not be determined.

- ~60% of *A. baumannii* from this set are carbapenem non-susceptible.
- ETX2514 effectively restores sulbactam activity. The addition of 4 mg/L ETX2514 decreased the sulbactam MIC_{90} from >32 mg/L to 2 mg/L.

Activity of Sulbactam-ETX2514 by Geographical Region and Infection Source

Geographical Region	**N**	**Sulbactam-ETX2514 (mg/L)**		
		MIC_{50}	**MIC_{90}**	**Range**
Europe	347	0.5	2	0.06 - 64
North America	262	0.5	2	≤0.03 - 8
Asia/South Pacific	119	0.5	2	0.06 - 16
Latin America	105	1	4	0.12 - 32
Middle East	15	1	2	0.25 - 2
Infection Source	**N**	**MIC_{50}**	**MIC_{90}**	**Range**
Respiratory	551	0.5	2	≤0.03 - 64
Urinary	134	0.5	2	0.06 - 64
Bloodstream	124	0.5	2	0.06 - 8
Intra-abdominal	39	0.5	1	0.12 - 4

- Sulbactam-ETX2514 potency was consistent across geographical regions and sources of infection.
- Sulbactam-ETX2514 maintained a MIC_{90} of 2 mg/L among the 489 carbapenem-non-susceptible isolates.
- Only 10 isolates (out of 848) had a MIC ≥ 8 mg/L.

- The 10 isolates with elevated MIC values were subjected to whole genome sequencing.
- 3 isolates encoded NDM-1, which ETX2514 does not inhibit.
- 6 isolates encoded mutations in PBP3, the target of sulbactam: PBP3 A515V (n=2), T526S (n=3), and T337I G523V (n=1).
- Further characterization of the mechanism of resistance is in progress.

Activity of Sulbactam-ETX2514 Against XDR *A. baumannii* Expressing OXA-237

- An outbreak of XDR *A. baumannii* infections occurred in 16 patients in 5 health care facilities in Oregon, USA between 2012-2014[3].
- All isolates belong to IC2 and encode for the class D β-lactamase OXA-237.
- 7 of 16 were resistant to colistin (43.8%)
- All 16 isolates were non-susceptible to sulbactam alone.
- Addition of 4 mg/L ETX2514 to sulbactam decreased MIC values to 2-8 mg/L (mode = 4 mg/L).
- Restoration of sulbactam activity by ETX2514 suggests it inhibits OXA-237

Isolate	**Resistance Mechanisms**	**MIC (mg/L)**			
		Sulbactam	**ETX2514**	**SUL-ETX2514**	**Imipenem**
ORAB01	OXA-237; OXA-66; ADC-30; ArmA	64	>64	4	8
ORAB02	OXA-237; OXA-66; ADC-30; ArmA	32	>64	4	8
ORAB03	OXA-237; OXA-66; ADC-30; ArmA	16	>64	4	8
ORAB0SC	OXA-237; OXA-66; ADC-30; ArmA	16	>64	4	8
ORAB06b	OXA-237; OXA-66; ADC-30	32	>64	8	8
ORAB08	OXA-237; OXA-66; ADC-30	32	>64	4	8
ORAB09	OXA-237; OXA-66; ADC-30	16	>64	4	8
ORAB12	OXA-237; OXA-66; ADC-30; ArmA	32	>64	2	8
ORAB13	OXA-237; OXA-66; ADC-30; ArmA	>64	>64	2	4
ORAB14	OXA-237; OXA-66; ADC-30; ArmA	8	>64	4	8
ORAB15	OXA-237; OXA-66; ADC-30	64	>64	8	8
ORAB16	OXA-237; OXA-66; ADC-30; ArmA	32	>64	2	8
ORAB17	OXA-237; OXA-66; ADC-30; ArmA	8	>64	2	8
ORAB18	OXA-237; OXA-66; ADC-30; ArmA	8	>64	4	8
ORAB21	OXA-237; OXA-66; ADC-30	32	>64	4	8
ORAB23	OXA-237; OXA-66; ADC-30	32	>64	2	8

Conclusions

- **ETX2514 restores sulbactam antibacterial activity against a global collection of 848 *A. baumannii* clinical isolates isolated in 2016 with a MIC_{90} of 2 mg/L.**
- **Activity of sulbactam-ETX2514 was consistent across regions, sources of infection and subset of resistance phenotypes.**
- **Less susceptible isolates either encode a metallo-β-lactamase or a mutation in PBP3.**
- **ETX2514 also restored sulbactam activity against a set of XDR *A. baumannii* OXA-237+ isolates from an recent outbreak in several health care facilities in Oregon.**
- **These data support development of ETX2514 in combination with sulbactam for the treatment of multidrug-resistant *A. baumannii*.**

References

1. Durand-Reville, T. et *al.* (2017) Nature Microbiol. 2:17104. **2.** CLSI M07-A10. 2015. **3.** Hujer *et al*. (2017) AAC 61: e00797-17. **4.** CLSI M100, 28th ed. 2018.

Presented at Microbe 2018, Atlanta, GA June 2018