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Sulbactam-durlobactam (ETX2514) Is Active Against Recent, Multidrug-Resistant *Acinetobacter baumannii* Clinical Isolates from the Middle East

S. McLeod[1], S. Moussa[1], M. Hackel[2], and A. Miller[1]
[1]Entasis Therapeutics, Waltham, MA and [2]IHMA, International Heath Management Associates, Schaumburg, IL, USA

Entasis Therapeutics
35 Gatehouse Dr.
Waltham, MA 02151
1-781-810-0121
alita.miller@entasistx.com

Abstract

Background: The incidence of infections caused by multidrug-resistant (MDR) *Acinetobacter baumannii* (*Ab*) is increasing at an alarming rate in certain regions of the world, including the Middle East. Sulbactam (SUL) has intrinsic antibacterial activity against *Ab*; however, the prevalence of β-lactamases in *Ab* has limited its therapeutic utility. Durlobactam (DUR, formerly ETX2514) is a diazabicyclooctane β-lactamase inhibitor with broad-spectrum activity against Ambler class A, C and D β-lactamases that restores SUL activity *in vitro* against MDR *Ab*. SUL-DUR is an antibiotic designed to treat serious infections caused by *Acinetobacter*, including multidrug-resistant strains, that is currently in Phase 3 clinical development. In global surveillance studies of >3600 isolates from 2012-2017, the MIC_{90} of SUL-DUR was 2 mg/L. Although surveillance systems to monitor MDR infections in the Middle East are currently being established, quantitative, prevalence-based data are not yet available. Therefore, the potency of SUL-DUR was determined against 190 recent, diverse *Ab* clinical isolates from this region.

Methods: 190 *Ab* isolates were collected between 2016 - 2018 from medical centers located in Israel (N = 47), Jordan (N = 36), Qatar (N = 13), Kuwait (N = 42), Lebanon (N = 8), Saudi Arabia (N = 24) and United Arab Emirates (N = 20). Seventy-five percent and 20.5% of these isolates were from respiratory and blood stream infections, respectively. Susceptibility to SUL-DUR and comparator agents was performed according to CLSI guidelines, and data analysis was performed using CLSI and EUCAST breakpoint criteria where available.

Results: This collection of isolates was 86% carbapenem-resistant and 90% sulbactam-resistant (based on a breakpoint of 4 mg/L). The addition of SUL-DUR (fixed at 4 mg/L) decreased the sulbactam MIC_{90} from 64 mg/L to 4 mg/L. Only 3 isolates (1.6%) had SUL-DUR MIC values of > 4 mg/L. This potency was consistent across countries, sources of infection and subsets of resistance phenotypes

Conclusions: SUL-DUR demonstrated potent antibacterial activity against recent clinical isolates of *Ab* from the Middle East, including MDR isolates. These data support the global development of SUL-DUR for the treatment of MDR *Ab* infections

Introduction

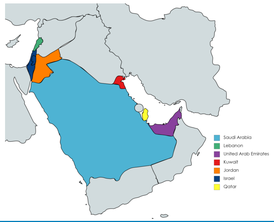
Sulbactam-durlobactam (SUL-DUR) is currently in Phase 3 clinical development for the treatment of infections caused by drug-resistant *Acinetobacter baumannii-calcoaceticus* complex (ABC) organisms. Sulbactam (SUL) is an approved β-lactamase inhibitor (BLI) with antibacterial activity against *Acinetobacter* spp. due to its inhibition of PBP3, an enzyme required for cell wall biosynthesis[1]. However, degradation of sulbactam by the β-lactamases present in most contemporary ABC isolates limits its clinical use. Durlobactam (DUR, ETX2514) is a diazabicyclooctane β-lactamase inhibitor (BLI) with potent activity against class A, C and D serine β-lactamases[2].
In global surveillance studies of over 1700 ABC isolates collected in 2016-2017, the addition of DUR reduced the MIC_{90} of SUL from 64 mg/L to 2 mg/L[3]. Here the activity of SUL-DUR was profiled against recent, diverse clinical *Acinetobacter baumannii* (*Ab*) isolates collected from seven countries located in the Middle East.

Methods

Broth microdilution susceptibility testing was conducted according to CLSI guidelines using cation-adjusted Mueller-Hinton broth[4]. Sulbactam-durlobactam was tested by dilution of sulbactam in the presence of a fixed concentration of 4 mg/L durlobactam. Testing of the 190 *Ab* isolates was performed at IHMA laboratories. Genomic DNA was extracted from select isolates and subjected to whole genome sequencing with an Illumina MiSeq V2 instrument and analysis using CLCBio Genomics Workbench v6.5 at Entasis Therapeutics.

Study Design

190 *Acinetobacter baumannii* (*Ab*) isolates from 7 countries and 21 medical centers
(Collected in IHMA surveillance program)

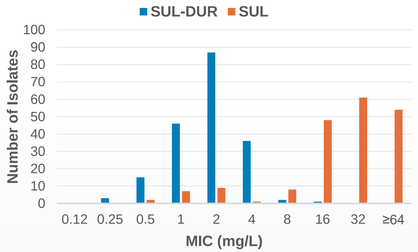


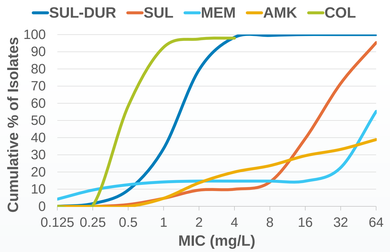
Country	N (sites)	N (isolates)
Israel	7	47
Jordan	3	36
Kuwait	3	42
Lebanon	3	8
Qatar	1	24
Saudi Arabia	3	24
U.A.E.	1	20

Year	N (isolates)
2016	45
2017	71
2018	74

Infection Source	N (isolates)
Respiratory	143
Bloodstream	39
Urinary	7
Intraabdominal	1

Durlobactam Restores Sulbactam Activity Against *Ab* Isolates from the Middle East





Antimicrobial	% Sensitive		Number (cumulative %) of isolates inhibited at MIC (mg/L)												
	CLSI*	EUCAST	≤0.03	0.06	0.12	0.25	0.5	1	2	4	8	16	32	64	>64
Sulbactam	NA	NA					2	7	9	1	8	48	61	**45**	9
							1.1	4.7	9.5	10	14.2	39.5	71.6	**95.3**	100
Sulbactam-Durlobactam	NA	NA				3	15	46	87	**36**	2	1			
						1.6	9.5	33.7	79.5	**98.4**	99.5	100			
Amikacin	30	24						9	17	12	7	11	7	11	**116**
								4.7	13.7	20	23.7	29.5	33.2	38.9	**100**
Cefepime	15	NA			1	2	1	4	6	6	9	8	**153†**		
					0.5	1.6	2.1	4.2	7.4	10.5	15.3	19.5	**100**		
Ciprofloxacin	11	0			5	9	3	4		3	**166†**				
					2.6	7.4	8.9	11.1		12.6	**100**				
Colistin	97	97				1	110	**65**	9	1		4†			
						0.5	58.4	**92.6**	97.4	97.9		100			
Imipenem	14	14				21	3		2			1	22	69	**72**
						11.1	12.6		13.7			14.2	25.8	62.1	**100**
Meropenem	15	15		1	7	10	6	3	1				15	62	**85**
				0.5	4.2	9.5	12.6	14.2	14.7				22.6	55.3	**100**
Minocycline	67	NA			21	10	21	18	21	36	33	**25**	5†		
					11.1	16.3	27.4	36.8	47.9	66.8	84.2	**97.4**	100		
Tigecycline	NA	NA	3	4	12	13	60	61	**29**	6	2†				
			1.6	3.7	10	16.8	48.4	80.5	**95.8**	98.9	100				

*Based on 2020 CLSI breakpoint criteria[5]. Colistin CLSI %S is based on %Intermediate NA = not available. MIC_{90}s are highlighted with blue squares. †Top concentration tested.

Activity of Sulbactam-Durlobactam by Demographic Sub-types

Country	N	Sulbactam-Durlobactam (mg/L)		
		MIC_{50}	MIC_{90}	Range
All	**390**	**2**	**4**	**0.25 - 16**
Israel	47	2	4	0.5 - 4
Jordan	36	2	4	0.5 - 4
Kuwait	42	2	4	0.25 - 16
Lebanon	26	1	2	0.25 - 32
Qatar	13	0.5	2	0.25 - 4
Saudi Arabia	24	2	4	0.5 - 8
United Arab Emirates	20	2	4	0.5 - 4
Resistance Phenotype*	**N**	**MIC_{50}**	**MIC_{90}**	**Range**
Carbapenem-NS	162	2	4	0.5 - 16
Colistin-resistant	5	--	--	1 - 4
MDR	57	2	4	1 - 16
XDR	3	--	--	2 - 4

*Carbapenem-NS, carbapenem non-susceptible; MDR, multidrug-resistant (non-susceptible to MEM, MIN, AMK); XDR, extremely drug-resistant (NS to MEM, MIN, AMK, CIP, FEP, SUL & R to COL)

Year	N	Sulbactam-Durlobactam (mg/L)		
		MIC_{50}	MIC_{90}	Range
2016	45	2	4	0.25 - 4
2017	71	2	4	0.5 - 8
2018	74	2	4	0.25 - 16
Infection Source	**N**	**MIC_{50}**	**MIC_{90}**	**Range**
Respiratory	143	2	4	0.25 - 16
Urinary	7	--	--	0.5 - 4
Bloodstream	39	2	4	0.5 - 4
Intra-abdominal	1	--	--	1

Activity of SUL-DUR was consistent across all the countries included in the study, years 2016-2018, infection source and antibiotic resistance phenotypes.

Antibiogram and Whole Genome Sequencing Results for Isolates with Elevated SUL-DUR MIC Values

Country	Organism	Year	Whole Genome Sequencing Results	MIC (mg/L)*						
				SUL-DUR	IPM	AMK	CIP	COL	MIN	TGC
Kuwait	*A. baumannii*	2018	ADC-73; TEM-1; OXA-23; OXA-66; PBP3 [A515V]	16	>64	>64	>4	1	16	2
Lebanon	*A. baumannii*	2017	ADC-73; TEM-1; OXA-23; OXA-66; PBP3 [A515V]; LpxA [M1K]	8	64	>64	>4	0.5	1	2
Saudi Arabia	*A. baumannii*	2018	ADC-73; TEM-1; OXA-23; OXA-66; PBP3 [A515V]; PmrB [L160F]	8	64	>64	>4	0.5	16	1

*IPM, imipenem; AMK, amikacin; CIP, ciprofloxacin; COL, colistin; MIN, minocycline; TGC, tigecycline.

- **The three isolates (3/190; 1.6%) with SUL-DUR MIC values ≥ 8 mg/L were subject to whole genome sequencing.**
- **All three isolates encoded a mutation near the active site of PBP3, the target of sulbactam inhibition.**
- **These results are consistent with global surveillance studies of SUL-DUR activity[3].**

Conclusions

- **Durlobactam restored sulbactam antibacterial activity against a collection of largely drug-resistant *A. baumannii* clinical isolates collected from countries in the Middle East between 2016-2018 with a MIC_{90} of 4 mg/L.**
- **Activity of sulbactam-durlobactam was consistent across seven countries located in the Middle East, years 2016-2018, and sources of infection.**
- **Less susceptible isolates encoded a mutation in PBP3 (target of sulbactam) and comprised <2% of the population.**
- **These data support development of sulbactam-durlobactam for the treatment of multidrug-resistant *A. baumannii*.**

References

1. Penwell *et al.* (2015) Antimicrob Agents Chemother. 59: 1680-1689 **2.** Durand-Reville, T. *et al.* (2017) Nature Microbiol. 2:17104 **3.** McLeod *et al.* (2020) Antimicrob Agents Chemother. 64:e02534-19
4. CLSI M07, 11th ed. 2018. **5.** CLSI M100, 30th ed. 2020.

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