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In Vitro Activity of Sulbactam-Durlobactam (ETX2514) Against Recent Global Clinical *Acinetobacter baumannii-calcoaceticus* Complex Isolates

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Abstract

Background: *Acinetobacter baumannii-calcoaceticus* complex (ABC) causes severe infections that are difficult to treat due to increasing resistance to antibacterial therapy. Sulbactam (SUL) has intrinsic antibacterial activity against ABC, but its clinical utility has been compromised by the prevalence of serine β-lactamases. Durlobactam (DUR, previously ETX2514) is a diazabicyclooctane β-lactamase inhibitor with potent activity against Ambler classes A, C and D serine β-lactamases that effectively restores SUL activity against ABC isolates. SUL-DUR is an antibiotic designed to treat serious infections caused by *Acinetobacter*, including multidrug-resistant strains, which is currently in Phase 3 clinical testing. The potency of SUL-DUR against geographically diverse ABC isolates collected in 2018 was measured.

Methods: 929 ABC isolates, including 698 *A. baumannii*, 13 *A. calcoaceticus*, 54 *A. nosocomialis*, and 164 *A. pittii*, were collected in 2018 from geographically diverse medical centers in the United States, Europe, Latin America, Israel and the Asia-Pacific region. Susceptibility testing was performed according to CLSI guidelines. Data analysis was performed using CLSI and EUCAST breakpoint criteria where available. Select isolates were subjected to whole genome sequencing with an Illumina MiSeq V2 instrument and analysis using CLCBio Genomics Workbench v6.5.

Results: In surveillance of 929 global isolates from 2018, the SUL-DUR MIC_{90} was 2 mg/L compared with 64 mg/L for SUL alone. This level of potency was consistent across species, regions, source of infection and subsets of resistance phenotypes. Fifty percent of the isolates were non-susceptible to carbapenems. Only 7 isolates (0.75%) had SUL-DUR MIC values >4 mg/L. Whole genome sequencing of these 7 isolates revealed that they either encoded the metallo-β-lactamase NDM-1, which DUR does not inhibit, or single amino acid substitutions near the active site of PBP3, the primary target of SUL.

Conclusions: SUL-DUR demonstrated potent antibacterial activity against recent, geographically diverse clinical isolates of ABC, including MDR isolates. These data support the potential utility of SUL-DUR for the treatment of antibiotic-resistant infections caused by ABC.

Introduction

The Gram-negative organisms collectively named the *Acinetobacter baumannii-calcoaceticus* complex (ABC) have emerged as serious pathogens[1]. The ABC complex includes *A. baumannii*, *A. nosocomialis*, *A. pittii* and *A. calcoaceticus*. *A. baumannii* are considered the most clinically important species of the complex due to their association with nosocomial outbreaks. Globally, the susceptibility of ABC to all antimicrobial agents has declined over the last 20 years[2].

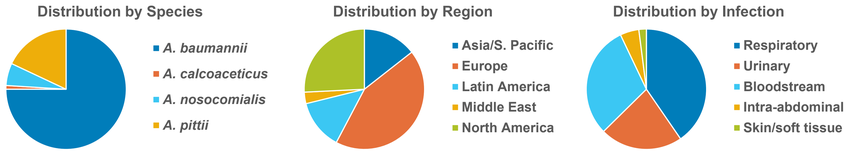
Sulbactam-durlobactam (SUL-DUR) is currently in Phase 3 clinical development for the treatment of infections caused by drug-resistant ABC organisms. Sulbactam (SUL) is an approved BLI with antibacterial activity against *Acinetobacter* spp. due to its inhibition of PBP3, an enzyme required for cell wall biosynthesis[3]. 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[4]. DUR protects SUL from degradation, restoring antibacterial activity against ABC organisms. Here we profile the activity of SUL-DUR against global ABC isolates collected in 2018.

Methods

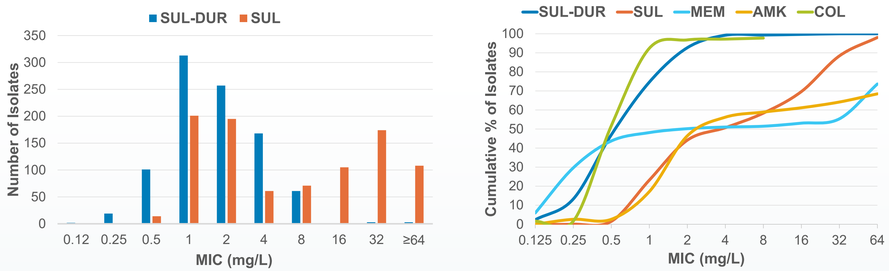
Broth microdilution susceptibility testing was conducted according to CLSI guidelines using cation-adjusted Mueller-Hinton broth[5]. Sulbactam-durlobactam was tested by dilution of sulbactam in the presence of a fixed concentration of 4 mg/L durlobactam. Testing of the 929 global ABC isolates was performed 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.

2018 Sulbactam-Durlobactam Global Surveillance Study Design

929 *Acinetobacter baumannii-calcoaceticus* complex (ABC) isolates
(Collected in 2018 global surveillance program by IHMA)



Durlobactam Restores Sulbactam Activity Against Geographically Diverse ABC from 2018



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					14	201	195	61	71	105	174	**90**	18
			0%	0%	0%	0%	2%	23%	44%	51%	58%	70%	88%	**98%**	100%
Sulbactam-Durlobactam	NA	NA	1	2	19	101	313	257	**168**	61	1	3	3		
			0%	0%	2%	13%	47%	75%	**93%**	99%	99%	100%	100%		
Amikacin	61	59				24		135	272	91	25	21	28	40	**293†**
			0%	0%	0%	3%	3%	17%	46%	56%	59%	61%	64%	68%	**100%**
Cefepime	48	NA		1		1	19	99	202	85	38	**484†**			
			0%	0%	0%	0%	2%	13%	35%	44%	48%	**100%**			
Ciprofloxacin	47	0		240		145	38	17	8	**481†**					
			0%	26%	26%	41%	46%	47%	48%	**100%**					
Colistin	97	97			15		465	**378**	41	4	21†				
			0%	0%	2%	2%	52%	**92%**	97%	97%	100%				
Imipenem	51	51		4	94	329	33	9	6	3	6	17	40	283	**105†**
			0%	0%	11%	46%	50%	50%	51%	51%	52%	54%	58%	89%	**100%**
Meropenem	50	50		7	48	220	131	41	19	8	4	15	21	170	**245†**
			0%	1%	6%	30%	44%	48%	50%	51%	51%	53%	55%	74%	**100%**
Minocycline	82	NA		361		121	92	73	50	66	**89**	77†			
			0%	39%	39%	52%	62%	70%	75%	82%	**92%**	100%			
Tigecycline	NA	NA	21	160	172	141	**388**	34	2	10	1				
			2%	19%	38%	53%	**95%**	99%	99%	100%	100%				

*Based on 2020 CLSI breakpoint criteria[6]. 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

Species	N	Sulbactam-Durlobactam (mg/L)		
		MIC_{50}	MIC_{90}	Range
All ABC	929	1	2	≤0.03 - 32
A. baumannii	698	1	2	0.06 - 32
A. calcoaceticus	13	0.5	1	0.12 - 1
A. nosocomialis	54	0.5	1	≤0.03 - 2
A. pittii	164	0.5	1	0.12 - 32
Resistance Phenotype*	**N**	**MIC_{50}**	**MIC_{90}**	**Range**
Carbapenem-NS	449	1	4	0.12 - 32
Colistin-resistant	30	2	4	0.5 - 4
MDR	139	2	4	0.5 - 4
XDR	19	2	4	0.5 - 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)

Geographical Region	N	Sulbactam-Durlobactam (mg/L)		
		MIC_{50}	MIC_{90}	Range
Europe	390	1	4	0.12 - 32
North America	256	0.5	1	0.06 - 8
Asia/South Pacific	132	01	2	0.12 - 32
Latin America	125	1	2	≤0.03 - 16
Middle East	26	1	2	0.25 - 32
Infection Source	**N**	**MIC_{50}**	**MIC_{90}**	**Range**
Respiratory	375	1	2	≤0.03 - 32
Urinary	206	0.5	2	0.12 - 4
Bloodstream	280	1	2	0.12 - 4
Intra-abdominal	47	1	2	0.25 - 16
Skin/soft tissue	21	1	4	0.25 - 16

Activity of SUL-DUR was consistent across species, geographical regions, sources of infection and subsets of resistance phenotypes, including MDR and XDR isolates.

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

Country	Organism	Whole Genome Sequencing Results	MIC (mg/L)						
			SUL-DUR	IPM	AMK	CIP	COL	MIN	TGC
Romania	*A. pittii*	ADC-71; OXA-533-like; TEM-1; **NDM-1**; AdeH [L155*]	32	>64	>64	>4	0.5	0.5	0.5
Romania	*A. pittii*	ADC-71; OXA-533-like; TEM-1; **NDM-1**; AdeH [L155*]	16	>64	>64	>4	1	1	1
Turkey	*A. baumannii*	ADC-30; OXA-23; OXA-66; **PBP3 [T526S]**; PmrA [G120*]	16	64	8	>4	0.5	0.5	0.5
Guatemala	*A. baumannii*	ADC-99-like; OXA-24; OXA-69 [TN insertion after Y215]; **PBP3 [T526S]**	16	>64	16	0.25	0.5	0.5	0.5
Israel	*A. baumannii*	ADC-76; OXA-58; OXA-68; **NDM-1;** 17kb del including *adeABCRS*	32	>64	>64	>4	0.5	2	0.5
United States	*A. baumannii*	ADC-30; OXA-66 [K42*]; OXA-72; **PBP3 [N377Y, T526S]**	8	64	64	>4	0.5	2	0.5
Philippines	*A. pittii*	ADC-18; OXA-500; PER-1; **NDM-1**	32	>64	32	2	≤0.25	0.25	0.25

- **The seven isolates (7/929; 0.8%) with SUL-DUR MIC values ≥ 8 mg/L were subject to whole genome sequencing.**
- **Four isolates encoded for the metallo-β-lactamase NDM-1, which durlobactam does not inhibit.**
- **Three isolates encoded a mutation near the active site of PBP3, the target of sulbactam inhibition.**

Conclusions

- **Durlobactam restores sulbactam antibacterial activity against a global collection of 929 ABC clinical isolates isolated in 2018 with a MIC_{90} of 2 mg/L.**
- **Activity of sulbactam-durlobactam was consistent across species, geographical regions, sources of infection and subsets of resistance phenotypes.**
- **Less susceptible isolates either encode a metallo-β-lactamase or a mutation in PBP3 (target of sulbactam).**
- **These data support development of sulbactam-durlobactam for the treatment of multidrug-resistant *A. baumannii*.**

References

1. El Chakhtoura *et al.* (2018) Expert Rev Anti Infect Ther. 16: 89-110 **2.** Gales *et al.* (2019) Open Forum Infect Dis. 6:S34-S46 3. Penwell *et al.* (2015) Antimicrob Agents Chemother. 59: 1680-1689 **4.** Durand-Reville, T. *et al.* (2017) Nature Microbiol. 2:17104. **5.** CLSI M07, 11th ed. 2018. **6.** CLSI M100, 30th ed. 2020.