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Characterization of Colistin-Resistant *Acinetobacter baumannii-calcoaceticus* Complex (ABC) Isolates from a Recent, Global Phase 3 Trial (ATTACK)

Samir H. Moussa, Sarah M. McLeod, and Alita A. Miller
Entasis Therapeutics, Waltham, MA, USA

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

Abstract

Background: Due to a lack of effective therapies, last-resort agents such as colistin are being used to treat drug-resistant ABC infections. Consequently, colistin-resistant (COL-R) ABC is becoming more common, with some countries such as Greece reporting rates of >50%[1]. The efficacy and safety of sulbactam-durlobactam (SUL-DUR) was recently compared to COL, both on a background of imipenem/cilastatin, in patients with ABC infections, including multidrug-resistant strains. SUL-DUR was non-inferior to colistin with respect to 28-day all-cause mortality (19 vs. 32.3%). SUL-DUR therapy resulted in higher clinical cure rates and significantly improved safety compared to COL. Here, we describe results for COL-R ABC in ATTACK.

Methods: Antibiotic susceptibility was determined by broth microdilution according to CLSI guidelines at IHMA, Inc (Schaumburg, IL). COL-R was defined as MIC ≥ 4 µg/ml. Next generation sequencing was performed using Nextera® libraries on an Illumina MiSeq system (San Diego, CA) at JMI Laboratories (North Liberty, IA) and Entasis Therapeutics. Assembly and analyses were performed using CLC Genomics Workbench.

Results: 17% (30 of 175) baseline ABC isolates from m-MITT (microbiologically modified Intent-to-Treat) patients were COL-R. All were extensively drug-resistant[2] and 26 were pan-drug resistant (PDR). Two additional ABC isolates became COL-R in patients with pneumonia who received COL therapy, both of whom did not survive to 28 days. Most came from 5 clinical sites: Hungary (N = 9), Russia (N = 7), Greece (N = 6), Israel (N = 3), Turkey (N = 2), Taiwan (N = 2) and Lithuania (N = 1). No COL-R ABC was found in China or the Americas. Sequencing analysis on selected isolates suggested sites in Hungary and Russia had clonal outbreaks, whereas others were non-clonal but closely related (>99%). SUL-DUR was highly active *in vitro* against COL-R ABC isolates, with an $MIC_{50/90}$ of 2/4 µg/ml. Of the 22 patients with COL-R ABC infections treated with SUL-DUR, 17 (77%) survived to 28 days with clinical and microbiological cure at test-of-cure (TOC).

Conclusions: A notable number of ABC infections in ATTACK were COL-R, most of which were PDR and SUL-DUR-sensitive. If approved, SUL-DUR could be an effective treatment for patients with these types of infections.

Introduction

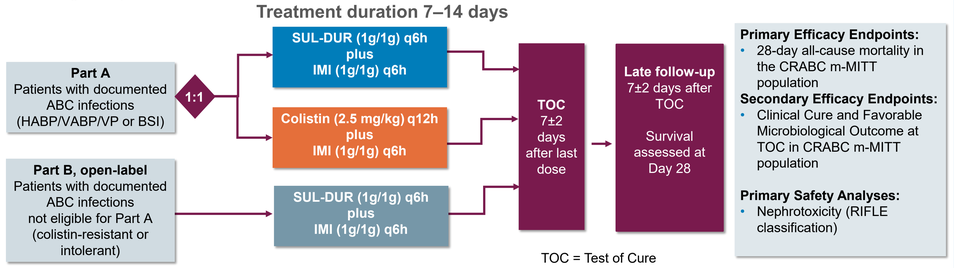
Acinetobacter baumannii-calcoaceticus complex (ABC) organisms can cause serious nosocomial infections that are difficult to treat due, in part, to rising rates of antimicrobial resistance. The lack of effective therapies has resulted in the use of colistin (COL) to treat ABC infections, leading to a rise in COL-resistant ABC[1].

Sulbactam-durlobactam (SUL-DUR) is a β-lactam/β-lactamase inhibitor (BL/BLI) combination currently being developed for the treatment of infections caused by ABC organisms including carbapenem-resistant and multidrug (MDR) strains. 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.

ATTACK was a Phase 3, randomized, controlled, noninferiority trial conducted to evaluate the efficacy and safety of SUL-DUR vs. COL, both in combination with imipenem/cilastatin (IMI) as background therapy, for patients with ABC infections. Treatment with SUL-DUR demonstrated lower mortality, higher clinical cure rates and greater microbiologically favorable outcomes in patients with carbapenem-resistant ABC infections. Here, the results for the COL-resistant ABC in ATTACK are presented.

ATTACK Trial Design

ATTACK was a Phase 3, multinational, randomised, controlled, noninferiority trial conducted to evaluate the efficacy and safety of SUL-DUR versus colistin, both in combination with imipenem/cilastatin as background therapy, for patients with serious infections due to ABC, including carbapenem-resistant ABC (CRABC) strains

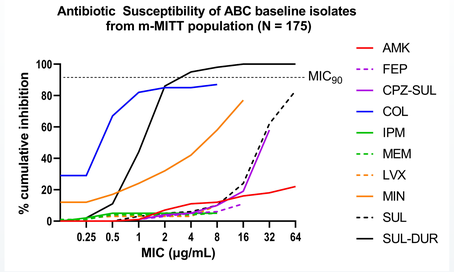


Primary Efficacy Endpoints:
- 28-day all-cause mortality in the CRABC m-MITT population

Secondary Efficacy Endpoints:
- Clinical Cure and Favorable Microbiological Outcome at TOC in CRABC m-MITT population

Primary Safety Analyses:
- Nephrotoxicity (RIFLE classification)

SUL-DUR Maintained *In Vitro* Activity Across Drug-Resistant Subsets of Baseline ABC Isolates from ATTACK



Antibiotic susceptibility was determined by broth microdilution according to CLSI guidelines[5,6]. AMK, amikacin; FEP, cefepime; CPZ-SUL, cefoperazone-sulbactam (2:1); COL, colistin; IPM, imipenem; LVX, levofloxacin; MEM, meropenem; MIN, minocycline; SUL, sulbactam; SUL-DUR, sulbactam-durlobactam

m-MITT ABC Isolates	N	%	SUL-DUR (µg/mL)		
			MIC_{50}	MIC_{90}	MIC Range
ALL	175	100	2	4	0.25 - 16
CARB-R	168	96	2	4	0.5 - 16
MDR	168	96	2	4	0.5 - 16
XDR	147	84	2	4	0.5 - 16
PDR	26	15	2	4	1 - 8
COL-R	30	17	2	4	0.5 - 8

- m-MITT patients were enrolled at 59 sites across 16 countries in the US, Latin America, Europe, Southeast Asia and China
- The majority of colistin-resistant ABC infections came from 5 clinical sites in Europe
- No colistin-resistant ABC isolates were detected at baseline in the Americas or China
- Most of the colistin-resistant ABC isolates were PDR but susceptible to SUL-DUR (preliminary breakpoint ≤ 4 µg/mL)

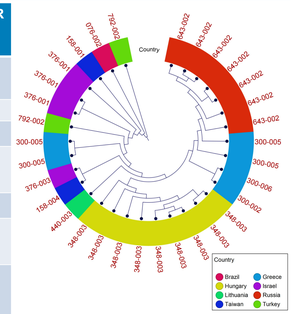
Outcomes for Patients with Colistin-Resistant ABC Infections Treated with Sulbactam-Durlobactam

CRABC m-MITT Patients	Part A SUL-DUR arm	Part A COL arm	Part B (all received SUL-DUR)	Patients with COL-R ABC Infections who received SUL-DUR
	% (n/N)	% (n/N)	% (n/N)	% (n/N)
28-Day All-Cause Mortality	19% (12/63)	32.3% (20/62)	18% (5/28)	22.7% (5/22)
Clinical Cure at TOC	61.9% (39/63)	40.3% (25/62)	71.4% (20/28)	77.3% (17/22)
Microbiological Favorable Outcome at TOC	68.3% (43/63)	41.9% (26/62)	78.6% (22/28)	77.3% (17/22)

Whole Genome Sequencing Results for Colistin-Resistant ABC Isolated from Patients in ATTACK

	Country	Clinical Site ID	No. of cases	MLST	β-lactamase genes	PmrB variants	Colistin MIC (µg/mL)	SUL-DUR MIC (µg/mL)
COL-R ABC at baseline	Hungary	348-003	9	ST^{Ox} 195 / ST^{Pa} 2	ADC-73, TEM-1, OXA-23, OXA-58, OXA-66	T13A, I23L, P96L, V117D, V227A, Q277R, N305Y, N353I, A408T	8 - >8	1 - 4
	Russia	643-002	7	ST^{Ox} 195 / ST^{Pa} 2	ADC-73, OXA-23, OXA-66	V227A	>8	2
	Greece	300-002	1	ST^{Ox} 436 / ST^{Pa} 2	ADC-73, TEM-1, OXA-23, OXA-66	A226V, V227A	>8	4
		300-005	4	ST^{Ox} 195 / ST^{Pa} 2 ST^{Ox} 425 / ST^{Pa} 2	ADC-73, OXA-23, OXA-66 ADC-73, TEM-1, OXA-23, OXA-66	V227A A226V, V227A	8 - >8	2 - 8
		300-006	1	ST^{Ox} 436 / ST^{Pa} 2	ADC-73, TEM-1, OXA-23, OXA-66	A226V, V227A	8 - >8	0.5
	Israel	376-001	3	ST^{Ox} 451 / ST^{Pa} 2 ST^{Ox} 457 / ST^{Pa} 2	ADC-73, TEM-1, OXA-23, OXA-66-like ADC-73, TEM-1, OXA-23, OXA-66	S14L, V227A, Q277K V227A, P233T	>8	2 - 4
	Turkey	792-002	2	ST^{Ox} 136 / ST^{Pa} 2 ST^{Ox} 229 / ST^{Pa} 25	ADC-73, TEM-1, OXA-23, OXA-66 ADC-26, OXA-23, OXA-64	V227A, Q277R V227A	>8 >8	2 2
	Lithuania	440-003	1	ST^{Ox} 195 / ST^{Pa} 2	ADC-73, TEM-1, OXA-23, OXA-66	V227A	>8	2
	Taiwan	158-001	1	ST^{Ox} 789	ADC-30, OXA-66, OXA-23	L153V, R181C, V227A	>8	8
		158-004	1	ST^{Ox} 1806 / ST^{Pa} 2	ADC-30, TEM-1, OXA-23, OXA-66	ΔL9-G12	4	0.5
Became COL-R	Brazil	076-002	1	ST^{Ox} 236 / ST^{Pa} 15	ADC-181, OXA-23, OXA-51	Baseline: none Day 7: K385I	0.5 >8	2 2
	Israel	376-002	1	ST^{Ox} 208 / ST^{Pa} 2	ADC-30, OXA-66, OXA-72	Baseline: none EOT: P170L	0.5 >8	2 4

MLST: Multi-locus sequencing type; ST^{Ox}: Oxford sequencing type scheme; ST^{Pa}: Pasteur sequencing type scheme; BLA: SUL-DUR, sulbactam-durlobactam; EOT, end of therapy



- All COL-R isolates in this study had previously described or new *pmrB* variants
- Isolates from sites with more than one COL-R infection were closely related or clonal

Outcomes of Patients Whose ABC Infections Became Resistant to Study Drug

Country	Infection type	Treatment arm	SUL-DUR MIC (µg/mL)		Colistin MIC (µg/mL)		mortality at 28 days	Clinical outcome			Microbiological Outcome		
			SCR	TOC	SCR	TOC		EOT	TOC	LFU	EOT	TOC	LFU
Greece	VABP	SUL-DUR	4	8	>8	>8	alive	cure	cure	fail	persistent	persistent	eradicated
Brazil	HABP	COL	2	2	0.5	>8	dead	cure	cure	fail	persistent	persistent	presumed persistent
Israel	VABP	COL	2	4	0.5	>8	dead	cure	fail	fail	persistent	persistent	presumed persistent

HABP, hospital-acquired bacterial pneumonia; VABP, ventilator-associated bacterial pneumonia; SUL-DUR, sulbactam-durlobactam; COL, colistin; SCR, screen; EOT, end of therapy; TOC, test of cure; LFU, late follow up; A microbiological outcome is presumed persistent if the clinical outcome was Fail, respectively, and no culture sample was obtained at that time

Conclusions

- A large number of ABC infections in ATTACK were colistin-resistant; most of which were in Europe.
- The majority of colistin-resistant isolates belonged to ST^{Pa} 2 (IC2) and had mutations in *pmrB,* consistent with previous reports.
- SUL-DUR maintained *in vitro* activity against colistin-resistant, XDR and PDR subsets of ABC isolates from ATTACK.
- Patients with COL-R infections treated with SUL-DUR had favorable clinical and microbiological outcomes.
- Two patients with respiratory infections in the COL arm became resistant to study drug; neither survived to 28 days.
- The single VABP patient in the SUL-DUR arm whose ABC infection showed elevated SUL-DUR MIC values over time survived to 28 days.
- If approved, SUL-DUR could be an important therapy option for patients with infections due to ABC, including MDR and COL-R isolates.

References

1. Nowak *et al.* (2017) JAC, 72: 3277-82 **2.** Magiorakis *et al.* (2012) CMI, 19:268-81 **3.** Penwell *et al.* (2015) Antimicrob Agents Chemother. 59: 1680-1689 **4.** Durand-Reville, T. *et al.* (2017) Nature Microbiol. 2:17104. **5.** CLSI M100, 30th ed. 2020. **6.** CLSI M07, 11th ed. 2018.

Disclosures: All authors are full-time employees of Entasis Therapeutics

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