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The Susceptibility of Sulbactam/ETX2514 and Comparators to Global Isolates of *Acinetobacter baumannii*

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Abstract

Background: The diazabicyclooctenone ETX2514 is a novel broad-spectrum serine ß-lactamase inhibitor that restores sulbactam (SUL) activity against resistant *Acinetobacter baumannii.* The combination sulbactam-ETX2514 (ETX2514SUL) has promising in vitro and in vivo activity against this organism. The purpose of this study was to evaluate the activity of ETX2514SUL and comparators against global, non-duplicate isolates of carbapenem-resistant *A. baumannii* (CRAB).

Materials and methods: Clinical isolates (n=246) were obtained from various body sites in patients and were collected in 37 countries and from six world regions between 2012-2016. Antimicrobial susceptibility testing was performed by broth microdilution in cation-adjusted Mueller–Hinton broth according to CLSI guidelines. The concentration ranges tested in 2-fold dilutions were: ETX2514SUL (fixed 4mg/L), 0.06/4–128/4 mg/L; imipenem/sulbactam/ETX2514 (1:1:2), 0.06/0.06/0.12–128/128/256mg/L; amikacin, 0.25–256 mg/L; colistin (COL), 0.06–128 mg/L; imipenem, 0.06–128 mg/L; meropenem, 0.06–128 mg/L; minocycline, 0.03–64 mg/L; and SUL, 0.06–128 mg/L. Susceptibility was determined using CLSI 2018 breakpoints where applicable. Based on core genome MLST results, isolates represented the 9 worldwide clonal lineages and included 184 isolates with blaOXA-23-like, 47 isolates with blaOXA-40-like, 3 isolates with blaOXA-58-like, 1 isolate with blaOXA-235-like, 3 isolates with NDM, one isolate with IMP, and 7 isolates with overexpression of intrinsic blaOXA-51.

Results: The ETX2514SUL $MIC_{50/90}$ values for all isolates were 1/4 and 2/4 mg/L, respectively. Comparatively, SUL, COL, minocycline, and amikacin $MIC_{50/90}$ values were 16/64, 0.5/1, 2/16, and ≥128/≥128 mg/L, respectively. Ten isolates were resistant to COL (4.1%), all of which had low ETX2514SUL MICs of ≤2/4 mg/L.

Conclusion: ETX2514SUL had excellent in vitro potency, including against isolates that were pan-resistant to SUL, imipenem/meropenem, COL, and amikacin, compared to other compounds. ETX2514SUL may be a therapeutic option for treatment of infections due to multidrug-resistant *A. baumannii*.

Introduction and Purpose

- Multidrug-resistant *Acinetobacter baumannii* is a growing threat leaving few therapeutic options. Carbapenem-resistance in *A. baumannii* mediated mainly through the action of intrinsic and acquired OXA-type enzymes is an increasing cause of concern (1).
- The diazabicyclooctenone ETX2514 is a novel broad-spectrum serine ß-lactamase inhibitor that restores sulbactam (SUL) activity against resistant *Acinetobacter baumannii.* The combination sulbactam-ETX2514 (ETX2514SUL) has promising in vitro and in vivo activity against this organism. The activity of ETX2514SUL was compared with anti-Acinetobacter reference drugs against well-defined *A. baumannii* isolates.

Methods

Bacterial isolates:

- 246 non-duplicate carbapenem-resistant *A. baumannii* (CRAb) isolates were collected from various body sites in patients from in 37 countries and from six world regions between 2012-2016.
- The isolates were subjected to whole genome sequencing (WGS) using the MiSeq Illumina platform and MLST types as well as carbapenem-resistance determinants were derived from WGS data.

Methods cont.

MIC testing:

- Broth microdilution (BMD) testing in cation-adjusted Mueller-Hinton broth was performed in accordance with CLSI guidelines (2).
- The antimicrobial agents and concentration ranges tested were: ETX2514SUL (ETX2514 fixed at 4mg/L), 0.06/4–128/4 mg/L; imipenem/sulbactam/ETX2514 (1:1:2), 0.06/0.06/0.12–128/128/256mg/L; amikacin, 0.25–256 mg/L; colistin, 0.06–128 mg/L; imipenem, 0.06–128 mg/L; meropenem, 0.06–128 mg/L; minocycline, 0.03–64 mg/L; and sulbactam, 0.06–128 mg/L. Susceptibility was determined using CLSI 2018 breakpoints where applicable.

Results

- The isolates represented the nine previously described international clonal lineages (1) and included 184 isolates with blaOXA-23-like, 47 isolates with blaOXA-40-like, 3 isolates with blaOXA-58-like, 1 isolate with blaOXA-235-like, 3 isolates with NDM, one isolate with IMP, and 7 isolates with overexpression of intrinsic blaOXA-51.
- The majority of *A. baumannii* isolates apart from being resistant to carbapenems were also resistant to amikacin and had high sulbactam MICs. The resistance rate to colistin was 4.1%.
- The ETX2514SUL $MIC_{50/90}$ values for all isolates were 1/4 and 2/4 mg/L, respectively. Comparatively, SUL, COL, minocycline, and amikacin $MIC_{50/90}$ values were 16/64, 0.5/1, 2/16, and ≥128/≥128 mg/L, respectively.
- Only nine isolates (3.6%) had ETX2514SUL MICs of ≥8/4 µg/mL.

Table 1. MIC distribution, MIC_{50} and MIC_{90} values of the 246 carbapenem-resistant *A. baumannii* isolates

Antimicrobial agent	≤0.06	0.125	0.25	0.5	1	2	4	8	16	32	64	≥128	MIC_{50}	MIC_{90}	MIC Range	%S	%I	%R
Amikacin				3	9	14	6	9	**9[a]**	25	20	165	≥128	≥128	0.5 - ≥128	20.3	10.2	69.5
Colistin		3	52	159	20	**2[a]**		2		3	4	1	0.5	1	0.125 - ≥128	95.9	-	4.1
ETX2514SUL[b,c]			**7**	**56**	**97**	**66**	**11**	**3**	**2**	**1**	**1**	**2**	**1**	**2**	**0.25 - 128/4**	**-**	**-**	**-**
Imipenem/SUL/ETX2514[b,d]			4	36	125	66	9	3		3			1	2	0.25 - 32	-	-	-
Imipenem						**0[a]**		8	5	49	121	63	64	128	8 - ≥128	0.0	0.0	100.0
Meropenem						**0[a]**		2	10	55	99	80	64	128	8 - ≥128	0.0	0.0	100.0
Minocycline	4	6	24	38	29	23	**27[a]**	35	52	4	4		2	16	≤ 0.06 - 64	61.4	14.2	24.4
Sulbactam[b]						2	11	43	68	80	36	6	16	64	2 - ≥128	-	-	-

[a] susceptible breakpoint values are indicated in boldface; [b] no CLSI breakpoint available; [c] depicted are sulbactam MIC values and [d] imipenem MIC values, respectively

References and Acknowledgements

1. Higgins PG et al. J Antimicrob Chemother. 2010; 65: 233-238

2. CLSI. M100 Performance Standards for Antimicrobial Susceptibility Testing, 28th Edition (2018).

This work was supported by an unrestricted grant from Entasis Therapeutics, Waltham, MA, USA.

Conclusions

- ETX2514SUL had excellent in vitro potency against *A. baumannii* isolates including those that were resistant to sulbactam, imipenem/meropenem, colistin, and amikacin, compared to other compounds.
- ETX2514SUL has the potential to become a useful addition to the limited armamentarium of drugs that can be used to treat this problem pathogen.