In-vitro activity of the novel fluorocycline TP-6076 against carbapenem non-susceptible *Acinetobacter baumannii*

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Abstract

Background: TP-6076 is a novel, fully synthetic fluorocycline antibiotic of the tetracycline class being developed for the treatment of serious infections, including those caused by multidrug-resistant (MDR) pathogens. The purpose of this study was to evaluate the activity of TP-6076 and comparators against global, non-duplicate isolates of carbapenem-resistant *Acinetobacter baumannii* (CRAb).

Materials and methods: Clinical isolates (n=326) were collected from various body sites in patients in ten mainly European countries from 2005-2016. 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: TP-6076, 0.008-16 mg/L; amikacin, 0.125-256 mg/L; colistin, 0.03-256; doxycycline, 0.03-32 mg/L; eravacycline, 0.008-16 mg/L; imipenem, 0.125-256 mg/L; levofloxacin, 0.03-64 mg/L; meropenem, 0.125-256 mg/L; minocycline, 0.06-128 mg/L; sulbactam, 0.06-128 mg/L; tigecycline, 0.03-64 mg/L; and tobramycin, 0.06-128 mg/L. Susceptibility was determined using CLSI 2015 breakpoints. Based on rep-PCR and MLST, isolates represented 8 worldwide clonal lineages and included 255 isolates with $bla_{\text{OXA-23-like}}$, 23 isolates with $bla_{\text{OXA-40-like}}$, 36 isolates with $bla_{\text{OXA-58-like}}$,10 isolates with overexpression of intrinsic $bla_{\text{OXA-51}}$, and 1 isolate with NDM-1.

Results: The TP-6076 $MIC_{50/90}$ values for all isolates were 0.06/0.25 mg/L. No isolate had MIC values >0.5mg/L. Comparatively, eravacycline, tigecycline, minocycline and doxycycline $MIC_{50/90}$ values were 0,5/1, 1/2, 4/8, and 32/≥64 mg/L, respectively. Of note, 44 isolates (13.5%) were resistant to colistin.

Conclusion: TP-6076 had excellent in vitro activity, including isolates that were pan-resistant to imipenem/meropenem, levofloxacin, amikacin/tobramycin, and colistin, compared to other compounds. TP-6076 may be a valuable therapeutic option for treatment of 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. Efflux does not significantly affect carbapenems, however it plays a role in the intrinsic resistance to fluoroquinolones, tetracyclines, aminoglycosides and macrolides.
- TP-6076 is a novel fully synthetic fluorocycline antibiotic of the tetracycline class with in vitro activity against key Gram-negative pathogens, including multidrug-resistant *Enterobacteriaceae* and *A. baumannii*. The activity of TP-6076 was compared with anti-Acinetobacter reference drugs against well-defined *A. baumannii* isolates.

Methods

Bacterial isolates:

- 326 non-duplicate carbapenem-resistant *A. baumannii* (CRAb) isolates were collected from various body sites in patients from eight European countries and Singapore between 2005 and 2015.
- The isolates were molecularly typed with repPCR (DiversiLab) (1) and MLST (2) and characterised for carbapenem-resistance mechanisms. They represented 6 of the 8 previously described international clonal lineages and included 255 isolates with $bla_{\text{OXA-23-like}}$,, 23 isolates with $bla_{\text{OXA-40-like}}$, 36 isolates with $bla_{\text{OXA-58-like,}}$ one isolate with $bla_{\text{OXA-23-like}}$ and $bla_{\text{OXA-58-like,}}$ one isolate with $bla_{\text{NDM-1}}$, and 10 isolates with overexpression of intrinsic $bla_{\text{OXA-51}}$.

Methods cont.

MIC testing:

- Broth microdilution (BMD) testing in cation-adjusted Mueller-Hinton broth was performed in accordance with CLSI guidelines (3).
- The antimicrobial agents and concentration ranges tested were TP-6076, 0.008-16 mg/L; amikacin, 0.125–256 mg/L; colistin, 0.03-256 mg/L; doxycycline, 0.03–32 mg/L; eravacycline, 0.008–16 mg/L; imipenem, 0.125–256 mg/L; levofloxacin, 0.03–64 mg/L; meropenem, 0.125–256 mg/L; minocycline, 0.06–128 mg/L; sulbactam, 0.06–128 mg/L; tigecycline, 0.03–64 mg/L; and tobramycin, 0.06–128 mg/L.
- MICs were interpreted according to the CLSI guidelines except where indicated.

Results

Table 1. MIC distribution, MIC_{50} and MIC_{90} values of the 326 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
TP-6076	204	84	36	2									0.06	0.25	≤ 0.06	-	0.5			
Amikacin				4	14	13	13	3	**15**[a]	12	35	217	≥128	≥128	0.5	-	≥128	19.0	3.6	77.3
Colistin			1	69	164	**48**[a]	12	11	2	1	4	14	1	4	0.25	-	≥128	86.5	-	13.5
Doxycycline	3	9	11	13	38	26	**5**[a]	4	13	67	137[c]		32	>32	≤ 0.06	-	≥64	32.2	1.2	66.6
Eravacycline[b]	15	26	48	165	60	11		1					0.5	1	≤ 0.06	-	8	-	-	-
Imipenem							2	10	76	183	48	7	32	64	8	-	128	0.0	0.6	99.4
Levofloxacin			2		1	**6**	35	102	136	19	20	5	16	32	0.25	-	≥128	2.8	10.7	86.5
Meropenem						**1**[a]	3	22	41	97	115	47	32	128	2	-	≥128	0.3	0.9	98.8
Minocycline	11	8	14	38	46	22	**73**[a]	82	31	1			4	8	≤ 0.06	-	32	65.0	25.2	9.8
Sulbactam[b]						3	13	52	88	123	40	7	32	64	2	-	≥128	-	-	-
Tigecycline[b]		5	27	48	157	68	20	1					1	2	0.125	-	8	-	-	-
Tobramycin		3	25	40	16	5	**5**[a]	13	21	29	6	163	64	≥128	0.125	-	≥128	28.8	4.0	67.2

[a] susceptible breakpoint values are indicated in boldface; [b] no CLSI breakpoint available; [c] ≥ 64 mg/L

Results cont.

- The majority of *A. baumannii* isolates apart from being resistant to carbepenems were also resistant to levofloxacin and aminoglycosides and had high sulbactam MICs. The resistance to colistin was 13.5%.
- The TP-6076 $MIC_{50/90}$ values for all isolates were 0.06/0.25 mg/L. No isolate had MIC values >0.5mg/L. Comparatively, eravacycline, tigecycline, minocycline and doxycycline $MIC_{50/90}$ values were 0.5/1, 1/2, 4/8, 32/≥64 mg/L, respectively.

References and Acknowledgements

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

2. Bartual SG et al. J Clin Microbiol. 2005; 43: 4382-4390.

3.CLSI. M100-S25 Performance Standards for Antimicrobial Susceptibility Testing_25th Informational Supplement (2015).

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Conclusions

- TP-6076 was the most potent antimicrobial against *A. baumannii* isolates, including those that were resistant to imipenem/meropenem, levofloxacin, sulbactam, and amikacin/tobramycin, compared to other compounds.
- TP-6076 has the potential to become a useful addition to the limited armamentarium of drugs that can be used to treat this problem pathogen.