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Comparison of Lysin CF-301 (exebacase) Activity Against *S. aureus* Isolates from Bacteremic Patients Enrolled in a Phase 2 Study (CF-301-102) to Contemporary Surveillance Isolates

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BACKGROUND

CF-301 (exebacase) is a novel, recombinantly-produced, bacteriophage-derived lysin (cell wall hydrolase) which is the first lysin to enter Phase 2 (Ph2) in the United States and is being studied for the treatment of *Staphylococcus aureus* (*S. aureus*) bacteremia including endocarditis. In the current study, we examined the in vitro activity of CF-301 against methicillin sensitive and methicillin resistant *S. aureus* (MSSA and MRSA) isolates from patients enrolled in the ongoing CF-301 'first in-patient' Ph2 study (NCT03163446) and in comparison to CF-301 MIC values reported in a recent global surveillance study.

PURPOSE

The objective of this work was to determine the MIC distribution of CF-301 against Ph2 clinical *S. aureus* isolates and to compare the data to contemporary clinical surveillance isolates. MIC values were determined by broth microdilution using a modified method approved for use with CF-301 by the Clinical and Laboratory Standards Institute (CLSI). The modification was based on the use of an antimicrobial susceptibility medium, caMHB supplemented with 25% horse serum and 0.5 mM DTT.

INTRODUCTION

With the increasing worldwide prevalence of antibiotic resistant bacteria, lysins are a promising novel alternative to small molecule antibiotics. Lysins are phage-encoded, recombinantly produced peptidoglycan hydrolases which are rapidly bacteriolytic when applied to target bacteria (see Fig. 1). CF-301 is an anti-staphylococcal lysin currently in Phase 2 of clinical development. Hallmark features of CF-301 include a rapid bacteriolytic effect against a range of *S. aureus* isolates, potent anti-biofilm activity, a low propensity for resistance, and synergy with antibiotics.

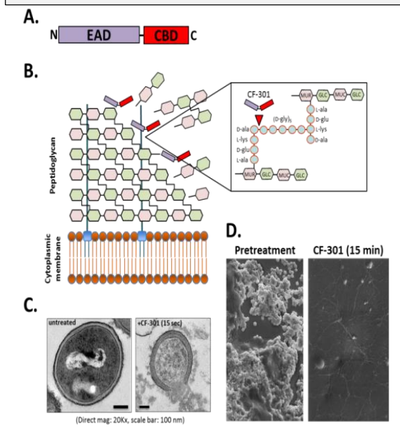

Fig. 1. Characteristics of lysins including CF-301. **(A)** Lysins have N-terminal enzymatically active domain (EAD) fused to a C-terminal cell wall binding domain (CBD). **(B)** Lysins rapidly degrade cell wall peptidoglycan to trigger lysis. The CF-301-sensitive bond is indicated. **(C)** Bacteriolytic effect of CF-301. **(D)** Eradication of catheter biofilm by CF-301.

METHODS

Patients with bacteremia including endocarditis were enrolled into Study CF-301-102 at study centers in the US and Guatemala between May 2017 and July 2018. Baseline isolates from blood cultures were collected prior to administration of CF-301. The activity of CF-301 activity against the first 82 baseline isolates of MSSA (n=53) and MRSA (n=29) was determined at a central laboratory (ACM Global Laboratories; Rochester, NY) using the CLSI-approved broth microdilution methodology for determining MIC values. Surveillance data for CF-301 was generated at the Clinical Microbiology Institute (Wilsonville, OR) against 556 MRSA and MSSA isolates collected from various infection sources at multiple hospitals from 2015-2017 in the US, Greece, Hungary, Italy, Chile and Columbia using the CLSI-approved methodology

RESULTS

Table 1. Cumulative frequency distribution of CF-301 MICs for Ph 2 clinical bacteremia and endocarditis isolates

Organism	Number of isolates	No. of isolates inhibited by CF-301 MIC (µg/mL) of:							MIC_{50} (µg/mL)	MIC_{90} (µg/mL)
		0.0625	0.125	0.25	0.5	1	2	4		
MSSA	53		2	12	26	13			0.5	1
MRSA	29			3	19	5	2		0.5	1

Table 2. Cumulative frequency distribution of CF-301 MICs from a surveillance study of clinical *S. aureus* isolates (collected from 2015-2018)

Organism	Number of isolates	No. of isolates inhibited by CF-301 MIC (µg/mL) of:							MIC_{50} (µg/mL)	MIC_{90} (µg/mL)
		0.0625	0.125	0.25	0.5	1	2	4		
MSSA	274			9	178	86	1		0.5	1
MRSA	282			17	166	95	4		0.5	1

- The $MIC_{50/90}$ for Ph 2 MSSA and MRSA isolates (collected between May 2017 and July 2018 were both 0.5/1 µg/mL (**Table 1**)
- The MIC range of Ph2 MSSA isolates was 0.125-1 ug/mL, whereas the MIC range of Ph 2 MRSA isolates was 0.25 to 2 µg/mL
- In the surveillance study we observed an $MIC_{50/90}$ (and range) of 0.5/1 µg/mL (0.25-2 µg/mL) for both the MSSA and MRSA isolates (**Table 2**)

CONCLUSIONS

- The activity of CF-301 against baseline *S. aureus* isolates from blood cultures obtained from bacteremic patients enrolled in the Ph2 study was similar to that observed in the global surveillance study
- $MIC_{50/90}$ values were the same among MSSA and MRSA demonstrating that CF-301 activity is not affected by methicillin susceptibility
- The MIC and range values reported here represent baseline susceptibility values for CF-301 against *S. aureus*
- Based on data from previously presented exposure target attainment animal studies, PK/PD modeling and preliminary non-clinical breakpoint assessments, we expect that strains with MIC values of ≤2 µg/mL will be susceptible to the clinical CF-301 dose (0.25mg/kg) currently under study in Ph2