Poster #
Sunday 530

CF-301 (Exebacase) Activity versus Contemporary *Staphylococcus aureus* Clinical Isolates from Six US Hospitals

M. M. TRACZEWSKI [1]*, A. Jandourek[2], J. Oh[2] and R. Schuch[2]
[1] Clinical Microbiology Institute, Wilsonville, OR and [2] ContraFect Corp., Yonkers, NY

Maria M. Traczewski BS, MT (ASCP).
Clinical Microbiology Institute
9725 SW Commerce Circle, Ste. A-1
Wilsonville, OR 97070
Tel: 503-682-3232
Email: mtrac@clinmicroinst.com

Abstract

Background: CF-301 (Exebacase) is a novel, recombinantly-produced, bacteriophage-derived lysin (cell wall hydrolase) which is in Phase 2 for the treatment of *S. aureus* bacteremia including endocarditis used in addition to standard of care antibiotics. Surveillance data on *S. aureus* clinical isolates collected in the United States are presented here.

Materials and Methods: CF-301 activity was tested against 300 clinical isolates of methicillin-resistant (150) and methicillin susceptible (150) *S. aureus* (MRSA and MSSA, respectively) collected from 6 US hospital systems in 2016 and 2017. Hospitals included Tufts New England Medical Center (Boston, MA), University of Rochester Medical Center (Rochester, NY), Mayo Clinic (Rochester, MN), University of Texas Hospital (San Antonio, TX), Providence Portland Medical Center (Portland, OR) and University of California Medical Center (Los Angeles, CA).The study was performed using an approved modification of the Clinical and Laboratory Standards Institute broth microdilution method (BMD) that uses CAMHB supplemented with 25% horse serum and 0.5 mM DL-dithiothreitol solution for minimal inhibitory concentration (MIC) testing with CF-301. Seven comparator agents were also tested including vancomycin, daptomycin, oxacillin, trimethoprim-sulfamethoxazole, cefazolin, linezolid and clindamycin.

Results:

S. aureus (no. of isolates)	Year	Number of isolates inhibited by CF-301 MIC (µg/mL) of: 0.125	0.25	0.5	1	2	4	MIC_{50} (µg/mL)	MIC_{90} (µg/mL)
MSSA (150)	2016-2017		2	91	57			0.5	1
MRSA (150)	2016-2017		5	108	37			0.5	1

MIC_{50} and MIC_{90} of *S. aureus* Comparator Agents (µg/mL)							
S. aureus	Van	Dap	Ox	Trim-Sul	Lin	Cefaz	Clinda
MSSA MIC_{50}	1	0.5	0.25	0.06	2	0.5	0.25
MSSA MIC_{90}	1	0.5	0.5	0.12	4	1	0.25
MRSA MIC_{50}	1	0.5	32	0.06	2	4	0.25
MRSA MIC_{90}	1	0.5	128	0.12	4	128	32

CF-301 MICs for both MSSA and MRSA ranged from 0.25 – 1 µg/mL. The CF-301 $MIC_{50/90}$ was 0.5/1 µg/mL for all isolates. $MIC_{50/90}$ values for all comparator antibiotics were observed within expected limits.

Conclusions The CF-301 $MIC_{50/90}$ for all clinical isolates (MSSA and MRSA) from a variety of human infection sites collected in 2016 – 2017 from six U.S. hospitals was 0.5/1 µg/mL. Overall, the findings of this surveillance study of contemporary clinical isolates are consistent with previously reported observations from a 2011 surveillance study of clinical isolates across the U.S.

Introduction

CF-301 is a novel recombinantly-produced bacteriophage-derived lysin (cell wall hydrolase) and is the first agent of this class in the US to enter Phase 2 clinical development for the treatment of bacteremia including endocarditis due to *S. aureus*.

Key Features of CF-301 lysin:

- **Rapid, potent, and targeted activity against pathogens, including antibiotic resistant strains**
- **Novel mechanism of action: peptidoglycan hydrolysis and osmotic lysis**
- **Synergy with conventional antibiotics**
- **Clearance of biofilms**
- **Low propensity to develop resistance**
- **Suppression of antibiotic resistance**

Materials and Methods

- **Clinical isolates were collected from six hospital laboratories located in Portland OR, Los Angeles CA, San Antonio TX, Rochester MN, Rochester NY and Boston MA. in 2016 and 2017.**
- **Isolates were stored frozen until use. Each site was asked to collect 25 MRSA and 25 MSSA.**
- **Broth microdilution MIC panels were prepared according to CLSI M7-A10 standard[1] and frozen at -70 ° C until use.**
- **Two-fold dilutions of CF-301 were prepared in cation-adjusted Mueller Hinton broth which was supplemented with 25% horse serum and 0.5 mM DL-Dithiothreitol solution.**
- **Comparator agents two-fold dilutions were prepared with CAMHB as per CLSI method and included oxacillin, vancomycin, daptomycin, linezolid, cefazolin, trimethoprim-sulfamethoxazole and clindamycin.**
- **In addition, screening tests for MRSA were performed. PBP2a tests were done on all isolates identified as oxacillin resistant.**
- **Isolate were subcultured from the freezer followed by a second subculture performed from the first plate 18 -20 hours prior to inoculating MIC tests**
- **Inocula were prepared using the direct inoculum method to match the density of a 0.5 McFarland standard.**
- **MIC panels were incubated in ambient air at 35 ° C.**
- **MICs were read after 16 -20 hours incubation except for oxacillin and vancomycin which were read after 24 hours incubation as per CLSI standard.**

Results

- **CF-301 MICs ranged from 0.25 to 1 µg/ml for all isolates of *S. aureus* tested.**
- **All MSSA and MRSA isolates from all sites had MIC_{50s} of 0.5 µg/ml**
- **All MSSA and MRSA isolates from all sites had MIC_{90s} of 1 µg/ml.**
- **Tables 1 and 2 present the geomean, MIC_{50}, MIC_{90} and range of MICs for CF-301 and all comparator agents tested**
- **Tables 3 and 4 present the percent inhibited at each MIC endpoint for CF-301 and all comparator agents tested.**
- **Figure 1 compares the MIC values of both MSSA and MRSA isolates.**

Conclusions

- **The CF-301 susceptibility of clinical isolates from US (obtained from 2016-2017) is nearly identical to that observed in the US isolates from 2011[3]**
- **The $MIC_{50/90}$ values described here represent baseline susceptibility values for CF-301**
- **We expect that isolates with $MIC_{90} \leq 1$ µg/ml will remain susceptible to the clinical CF-301 dose of 0.25 mg/kb based on previously presented exposure target attainment animal studies and PK/PD modeling[4]**
- **Continued surveillance will be important to delineate the susceptibility profile of CF-301**

Table 1. *Staphylococcus aureus* oxacillin resistant MIC analysis

Species	N	Drug	Geometric Mean	Mode	Minimum	Maximum	Range (Log2 Dilutions)	MIC50	MIC90
***S. aureus* oxacillin resistant**	150	CF-301 MIC	0.645	0.5	0.25	1	3	0.5	1
	150	Vancomycin MIC	0.883	1	0.5	2	3	1	1
	150	Daptomycin MIC	0.538	0.5	0.25	2	4	0.5	0.5
	150	Oxacillin MIC	34.615	32	0.5	128	9	32	128
	150	Trimethoprim-Sulfamethoxazole MIC	0.101	0.06	0.06	32	10	0.06	0.12
	150	Linezolid MIC	2.173	2	1	4	3	2	4
	150	Cefazolin MIC	8.225	4	0.5	128	9	4	128
	150	Clindamycin MIC	0.725	0.25	0.12	32	9	0.25	32

Table 2. *Staphylococcus aureus* oxacillin susceptible MIC analysis

Species	N	Drug	Geometric Mean	Mode	Minimum	Maximum	Range (Log2 Dilutions)	MIC50	MIC90
***S. aureus* oxacillin resistant**	150	CF-301 MIC	0.580	0.5	0.25	1	3	0.5	1
	150	Vancomycin MIC	0.737	1	0.5	1	2	1	1
	150	Daptomycin MIC	0.489	0.5	0.25	1	3	0.5	0.5
	150	Oxacillin MIC	0.309	0.25	0.06	2	6	0.25	0.5
	150	Trimethoprim-Sulfamethoxazole MIC	0.079	0.06	0.06	4	7	0.06	0.12
	150	Linezolid MIC	2.567	2.0	1	4	3	2.0	4
	150	Cefazolin MIC	0.437	0.5	0.12	1	4	0.5	1
	150	Clindamycin MIC	0.239	0.25	0.12	32	9	0.25	0.25

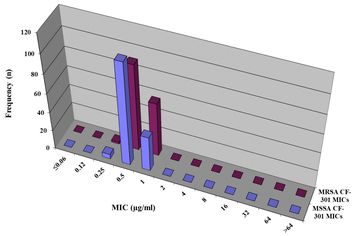
Table 3. *Staphylococcus aureus* oxacillin resistant Percent Inhibited by MIC

Species	MIC (µg/ml)	CF-301 MIC Frequency	CF-301 MIC Cumulative % Inhibited	Vancomycin MIC Frequency	Vancomycin MIC Cumulative % Inhibited	Daptomycin MIC Frequency	Daptomycin MIC Cumulative % Inhibited	Oxacillin MIC Frequency	Oxacillin MIC Cumulative % Inhibited	Trimethoprim-Sulfamethoxazole MIC Frequency	Trimethoprim-Sulfamethoxazole MIC Cumulative % Inhibited	Linezolid MIC Frequency	Linezolid MIC Cumulative % Inhibited	Cefazolin MIC Frequency	Cefazolin MIC Cumulative % Inhibited	Clindamycin MIC Frequency	Clindamycin MIC Cumulative % Inhibited
***S. aureus* oxacillin resistant**	0.015																
	0.030																
	0.060									112	74.7%						
	0.12									24	90.7%					28	18.7%
	0.25	2	1.3%			1	0.7%			3	92.7%					84	74.7%
	0.5	91	62.0%	29	19.3%	134	90.0%	2	1.3%	1	93.3%			2	1.3%	1	75.3%
	1	57	100.0%	119	98.7%	13	98.7%	1	2.0%	1	94.0%	4	2.7%	5	4.7%		
	2			2	100.0%	2	100.0%	1	2.7%	1	94.7%	124	85.3%	21	18.7%		
	4											22	100.0%	50	52.0%		
	8							10	9.3%	1	95.3%			31	72.7%		
	16							25	26.0%	0	95.3%			8	78.0%		
	>16 or 32							57	64.0%	7	100.0%			7	82.7%	37	100.0%
	64							25	80.7%					5	86.0%		
	>64 or 128							29	100.0%					21	100.0%		
	Totals	150	100.0%	150	100.0%	150	100.0%	150	100.0%	150	100.0%	150	100.0%	150	100.0%	150	100.0%

Table 3. *Staphylococcus aureus* oxacillin susceptible Percent Inhibited by MIC

Species	MIC (µg/ml)	CF-301 MIC Frequency	CF-301 MIC Cumulative % Inhibited	Vancomycin MIC Frequency	Vancomycin MIC Cumulative % Inhibited	Daptomycin MIC Frequency	Daptomycin MIC Cumulative % Inhibited	Oxacillin MIC Frequency	Oxacillin MIC Cumulative % Inhibited	Trimethoprim-Sulfamethoxazole MIC Frequency	Trimethoprim-Sulfamethoxazole MIC Cumulative % Inhibited	Linezolid MIC Frequency	Linezolid MIC Cumulative % Inhibited	Cefazolin MIC Frequency	Cefazolin MIC Cumulative % Inhibited	Clindamycin MIC Frequency	Clindamycin MIC Cumulative % Inhibited
***S. aureus* oxacillin susceptible**	0.015																
	0.030																
	0.060							4	2.7%	107	71.3%						
	0.12							18	14.7%	37	96.0%			6	4.0%	44	29.3%
	0.25	5	3.3%	0	0.0%	11	7.3%	63	56.7%	2	97.3%			35	27.3%	99	95.3%
	0.5	108	75.3%	66	44.0%	133	96.0%	58	95.3%	2	98.7%			91	88.0%	2	96.7%
	1	37	100.0%	84	100.0%	6	100.0%	6	99.3%	0	98.7%	2	1.3%	18	100.0%		
	2							1	100.0%	1	99.3%	92	62.7%				
	4									1	100.0%	56	100.0%				
	8																
	16																
	>16 or 32															5	100.0%
	64																
	>64 or 128																
	Totals	150	100.0%	150	100.0%	150	100.0%	150	100.0%	150	100.0%	150	100.0%	150	100.0%	150	100.0%

Figure 1. *S. aureus* oxacillin susceptibile and resitant CF-301 MICs



Acknowledgement

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