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EXPERIMENTAL THERAPEUTICS

Antimicrobial Activity of Exebacase (Lysin CF-301) against the Most Common Causes of Infective Endocarditis

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ABSTRACT Exebacase, a recombinantly produced lysin (cell wall hydrolase), and comparator antibiotics were tested by the broth microdilution method against strain sets of *Staphylococcus* and *Streptococcus* spp., which are the most common causes of infective endocarditis in humans. Exebacase was active against all *Staphylococcus* spp. tested, including *S. aureus* and coagulase-negative staphylococci ($MIC_{50/90}$, 0.5/1 μg/ml). Activity against *Streptococcus* spp. was variable, with *S. pyogenes*, *S. agalactiae*, and *S. dysgalactiae* ($MIC_{50/90}$, 1/2 μg/ml) among the most susceptible.

KEYWORDS *Staphylococcus*, *Streptococcus*, antimicrobial activity, exebacase, infective endocarditis, lysin

Infective endocarditis (IE) is a life-threatening disease with a poor prognosis, reflected by hospital mortality rates of up to 20 to 40% despite the use of high-dose and long-term intravenous antibiotic therapy (1, 2). Surgical intervention is frequently required in many cases to eradicate the infection and preserve cardiac function (3).

A significant challenge in the treatment of IE concerns the ability of colonizing bacteria, primarily *Staphylococcus* and *Streptococcus* spp., to adhere to cardiac surfaces and form biofilm-like vegetations which can be refractory to antibiotics and immune surveillance, resulting in persistent and relapsing infections (4–6). Current IDSA guidelines recommend either vancomycin or daptomycin for the treatment of IE caused by methicillin-resistant *Staphylococcus aureus* (MRSA) in adults (3, 7); however, vancomycin has been associated with poor clinical outcomes (4, 8), and daptomycin, the most recent drug approved by the U.S. Food and Drug Administration (in 2006) for *S. aureus* bloodstream infections (9), exhibited a clinical cure rate of 44.2% in a phase 3 trial for *S. aureus* bacteremia and endocarditis (10). New and more effective antimicrobial agents are required to address the challenging characteristics of bacteria in biofilm, in particular high cell densities, low growth rates, "persister" subpopulations, and other protective mechanisms (3, 4, 11).

One promising approach, now under clinical development to target bacteria growing in a biofilm, is based on a new antimicrobial class of direct lytic agents (DLAs), which includes a large family of bacteriophage-encoded cell wall hydrolases called lysins (12–14). As recombinantly expressed and purified enzymes, lysins elicit rapid bactericidal effects on specific bacterial organisms. Exebacase (formerly CF-301) is a potent antistaphylococcal lysin, with distinguishing features that include a low propensity for resistance, synergy with conventional antibiotics, no antibiotic cross-resistance, an extended postantibiotic effect, and, significantly, potent activity against Gram-positive bacteria growing in biofilms (15–21). Exebacase is, furthermore, the first DLA to report results from a phase 2 (Ph2) clinical trial, which demonstrated 42.8% higher clinical responder rates with a single dose of exebacase used in addition to standard-of-care antibiotics (SOC) versus SOC alone for the treatment of MRSA bacteremia, including endocarditis (18, 22). Exebacase represents a novel approach to treating IE caused by

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TABLE 1 Review of data from seven studies examining the causative agents of infective endocarditis in humans

Organism	Microorganisms identified by blood culture (%) in various studies[a]						
	Yuan (39), *n* = 167	Murdoch et al. (2), *n* = 2,781	Farag et al. (40), *n* = 360	Munoz et al. (41), *n* = 1,804	Xu et al. (42), *n* = 105	Selton-Suty et al. (43), *n* = 497	Yombi et al. (44), *n* = 212
S. aureus	44.3	31.0	24.7	40.3	10.4	26.6	23.6
S. epidermidis	1.8		6.4				6.1
S. lugdunensis	1.8		1.4				0.9
Other CoNS[b]	3.0	11.0	4.6	16.7*	12.4*	9.7*	5.3
Streptococcus viridans[c]	6.6	17.0	38.6	12.3	58.1		16.0
S. agalactiae	3.0		1.4				2.4
S. pyogenes							0.9
S. pneumoniae			0.6				
S. gallolyticus		6	6.1	6.4		12.5	7.1
"Oral" streptococci[d]						18.7	
Streptococcus group G							1.4
Enterococcus faecalis	6.6		11.1		4.8		11.8
Enterococcus spp.[e]				12.7			

[a]References for each study are indicated (*n*, number of patients in each study). A set of references were chosen based on a literature review of PubMed performed in 2018 focusing on the most common causes of IE that provided an overall prevalence of each pathogen that was encountered. The findings are consistent with the general understanding of pathogens associated with IE (3, 4, 38). *, studies that grouped all CoNS species together.

[b]Some studies here distinguish *S. epidermidis* and *S. lugdunensis* from other more infrequent CoNS organisms associated with IE, including *S. capitis*, *S. warneri*, and *S. haemolyticus* (25, 40, 45).

[c]The viridans group streptococci causing IE include *S. mitis*, *S. sanguinis*, *S. mutans*, *S. salivarius*, *S. gordonii*, *S. intermedius*, and *S. anginosus* (28, 46–48).

[d]Viridans streptococci are referred to as oral streptococci in the indicated study.

[e]Species not provided; however, *E. faecalis* causes ~97% of IE cases associated with enterococci (3).

S. aureus that leverages both the antibiofilm and bactericidal activities of exebacase and the potent activities of antibiotics against planktonic cells.

In the present study, the *in vitro* activity of exebacase and comparator antibiotics (i.e., daptomycin and vancomycin) were evaluated against a range of bacterial species most commonly associated with IE (Table 1). *Staphylococcus aureus* is the primary cause of IE, in addition to other common pathogens such as coagulase-negative staphylococci, enterococci, viridans group streptococci, and other streptococci. Whereas the potent activity of exebacase against *S. aureus* is well described, only limited data exist for the other staphylococcal and streptococcal pathogens (15, 16, 21). The purpose of this study was to provide a greater understanding of exebacase activity among the main staphylococcal and streptococcal pathogens associated with IE.

The strains and isolates used in this study were acquired from collections and repositories in the United States, Europe, and Asia and were confirmed at the species level by each source. The isolates were isolated from a range of infection types, including bacteremia (and endocarditis), skin and soft tissue infections, and respiratory infections (see Tables S1 and S2 in the supplemental material). A range of infections types were included to ensure a sufficient number of isolates for each target species.

The MICs of exebacase against staphylococci were determined by broth microdilution (BMD) (23) using a nonstandard antimicrobial susceptibility testing (AST) medium comprised of cation-adjusted Mueller-Hinton broth (CAMHB) supplemented with horse serum (Sigma-Aldrich) and dithiothreitol (Sigma-Aldrich) to final concentrations of 25% and 0.5 mM, respectively. This medium, referred to as CAMHB-HSD, was approved for use in exebacase AST by the Clinical and Laboratory Standards Institute (CLSI) AST Subcommittee, based on the acceptance of quality control (QC) ranges determined for the QC strains ATCC 29213 and ATCC 29212 in CLSI M23 studies using CAMHB-HSD (24). Additional supplementation with 2.5% lysed horse red blood cells (Remel; Thermo Fisher) was included for analyses of streptococcal isolates, as recommended by the CLSI (23). Daptomycin (Sigma-Aldrich) and vancomycin hydrochloride (Sigma-Aldrich) were analyzed in parallel (using the same inoculum), following the reference BMD method for each (23).

Exebacase activity was first confirmed using sets of 73 methicillin-susceptible *S. aureus* (MSSA) and 74 MRSA isolates, which demonstrated $MIC_{50/90}$ values of 0.5/

TABLE 2 Susceptibility of *Staphylococcus* species to exebacase and comparator antibiotics[a]

Organism	*n*	Exebacase			DAP			VAN		
		MIC_{50}[a]	MIC_{90}	Range	MIC_{50}	MIC_{90}	Range	MIC_{50}	MIC_{90}	Range
S. aureus (MSSA)	73	0.5	0.5	0.25–1	0.25	0.25	0.125–0.5	1	1	0.5–1
S. aureus (MRSA)	74	0.5	1	0.5–2	0.25	0.5	0.125–1	1	1	1–2
S. epidermidis[b]	52	0.5	0.5	0.125–2	ND	ND	ND	ND	ND	ND
S. lugdunensis	46	1	1	0.25–2	0.5	1	0.25–2	1	1	0.5–2
S. haemolyticus	34	0.5	1	0.25–2	0.5	1	0.25–2	1	2	0.5–4
S. capitis	13	1	2	0.25–4	0.5	1	0.25–1	1	1	0.5–2
S. warneri	21	0.5	1	0.06–1	0.5	2	0.25–2	1	2	0.25–2

[a]MIC values are indicated in μg/ml. DAP, daptomycin; VAN, vancomycin.
[b]MIC values for DAP and VAN data were not determined (ND) for *S. epidermidis*.

0.5 μg/ml and 0.5/1 μg/ml and ranges of 0.25 to 1 μg/ml and 0.5 to 2 μg/ml, respectively (Table 2). Similar levels activity were next observed for each coagulase-negative staphylococcal species, including *Staphylococcus epidermidis* ($MIC_{50/90}$ = 0.5/0.5 μg/ml), *Staphylococcus lugdunensis* ($MIC_{50/90}$ = 1/1 μg/ml), *Staphylococcus haemolyticus* ($MIC_{50/90}$ = 0.5/1 μg/ml), *Staphylococcus capitis* ($MIC_{50/90}$ = 1/2 μg/ml), and *Staphylococcus warneri* ($MIC_{50/90}$ = 0.5/1 μg/ml). *Staphylococcus hominis*, only rarely associated with IE (25), was tested (n = 2 strains) and demonstrated exebacase MIC values of 0.125 and 0.25 μg/ml (data not shown). Other staphylococcal species tested included *Staphylococcus pseudintermedius* (MIC = 0.25 μg/ml, each of n = 6 isolates), *S. sciuri* (MIC = 2 μg/ml, n = 3 isolates), *Staphylococcus simulans* (MIC = 0.125 μg/ml, n = 1 isolate), and *Staphylococcus hyicus* (MIC = 0.25 μg/ml, n = 1 isolate). MICs for daptomycin and vancomycin were observed with ranges of 0.125 to 2 μg/ml and 0.5 to 4 μg/ml, respectively, for all staphylococci tested, consistent with expected ranges (26, 27).

The majority of viridans streptococci tested, in addition to *Streptococcus pneumoniae* and *Enterococcus faecalis* (formerly group D streptococcus), exhibited high MICs for exebacase, with values ranging up to >512 μg/ml (Table 3). Notable exceptions included *Streptococcus intermedius*, *Streptococcus pyogenes* (Lancefield group A), *Streptococcus agalactiae* (Lancefield group B), and *Streptococcus dysgalactiae* (Lancefield group G), with MIC ranges of 0.06 to 0.5, 0.5 to 4, 0.25 to 4, and 1 to 2 μg/ml, respectively. Unlike many of the viridans streptococci and *E. faecalis* which primarily cause subacute IE, *S. intermedius* (a viridans group species) and both *S. agalactiae* and *S. dysgalactiae* are, interestingly, associated with the more aggressive acute disease caused by staphylococci and resulting in rapid destruction of the endocardium (28–32).

Overall, the exebacase data presented here demonstrated promising *in vitro* anti-

TABLE 3 Susceptibility of *Streptococcus* and *Enterococcus* species to exebacase and comparator antibiotics[a]

Organism	*Streptococcus* group	*n*	Exebacase			DAP			VAN		
			MIC_{50}[a]	MIC_{90}	Range	MIC_{50}	MIC_{90}	Range	MIC_{50}	MIC_{90}	Range
S. anginosus	Viridans	10	32	64	1–64	0.5	0.5	0.25–0.5	0.5	1	0.5–1
S. gordonii	Viridans	11	4	8	0.5–8	0.5	0.5	0.25–1	0.5	1	0.5–1
S. mitis	Viridans	17	2	8	0.5–64	0.5	1	0.125–1	0.5	0.5	0.25–0.5
S. mutans	Viridans	22	32	64	1–>64	0.5	1	0.25–8	1	1	0.25–1
S. oralis	Viridans	15	4	64	0.5–64	0.5	0.5	0.25–1	0.5	1	0.5–1
S. salivarius	Viridans	12	2	8	0.5–8	0.25	0.5	0.06–0.5	0.5	0.5	0.25–0.5
S. sanguinis	Viridans	15	4	16	2–32	0.25	1	0.06–1	0.5	0.5	0.5–2
S. intermedius[b]	Viridans	10	0.25	0.5	0.06–0.5	ND	ND	ND	ND	ND	ND
S. gallolyticus	Bovis	19	64	>512	0.25–>512	0.125	0.25	0.06–0.5	0.25	0.5	0.25–0.5
S. pyogenes	A	100	1	2	0.5–4	0.03	0.06	0.016–0.06	0.5	0.5	0.25–0.5
S. agalactiae	B	97	1	2	0.25–4	0.125	0.25	0.125–0.25	0.5	0.5	0.25–0.5
S. dysgalactiae	G	22	1	2	1–2	0.125	0.25	0.06–0.5	0.5	0.5	0.25–1
S. pneumoniae		59	4	32	1–64	0.125	0.5	0.06–0.25	0.25	0.5	0.25–0.5
E. faecalis	D (formerly)	18	16	64	1–256	0.5	0.5	0.25–0.5	1	2	0.5–2

[a]MIC values are indicated in μg/ml. DAP, daptomycin; VAN, vancomycin.
[b]MIC values for DAP and VAN data were not determined (ND) for *S. intermedius*.

microbial activity, with MIC values of ≤2 μg/ml against all staphylococcal and a subset of streptococcal species. Importantly, data from exposure target attainment animal studies, pharmacokinetic/pharmacodynamic modeling, and preliminary nonclinical breakpoint assessments indicate that strains with MIC values of ≤2 μg/ml are expected to be susceptible to the clinical dose of exebacase (0.25 mg/kg) studied in Ph2 (33–35). Our findings are particularly significant considering that staphylococci and streptococci are the most frequently isolated Gram-positive cocci isolated in native and prosthetic valve infections (3, 4, 36–38).

The concept of combining the potent antibiofilm and bactericidal activities of lysins with the well-understood strengths of antibiotics represents a completely novel approach that is under investigation in a Ph2 clinical trial for the treatment of *S. aureus* bacteremia and endocarditis with exebacase in addition to conventional antibiotics. The trial is expected to provide a proof of concept for the novel treatment approach.

SUPPLEMENTAL MATERIAL

Supplemental material for this article may be found at https://doi.org/10.1128/AAC.01078-19.

SUPPLEMENTAL FILE 1, PDF file, 1.1 MB.

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