Exebacase: A Novel Approach to the Treatment of Staphylococcal Infections

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Abstract
Lysins are bacteriophage-derived enzymes that degrade essential components of bacteria. Exebacase (Lysin CF-301) is an attractive antimicrobial agent because it demonstrates rapid bacteriolytic activity against staphylococcal species, including Staphylococcus aureus, has a low resistance profile, eradicates biofilms, and acts synergistically with other antibiotics. Combinations including exebacase and standard of care antibiotics represent an alternative to antibiotic monotherapies currently used to treat invasive staphylococcal infections. This manuscript reviews what is known about exebacase and explores how this novel agent may be used in the future to treat human bacterial pathogens.

Key Summary Points
- Lysins have emerged as antimicrobial agents owing to their potency and specificity for bacterial pathogens in comparison with antibiotics.
- Exebacase is a first-in-class anti-staphyloccocal lysin that has applications for the treatment of a variety of clinical syndromes.
- Exebacase is rapidly bacteriostatic, eradicates biofilms, and has demonstrated clinical efficacy in combination with other antibiotics against a variety of staphylococcal pathogens that produce syndromes ranging from bacteremia to osteomyelitis.

1 Introduction
Lysins are enzymes produced by bacteriophages to cleave the bacterial host’s cell wall during the final stage of the lytic cycle, releasing newly replicated virus from the bacteria [1–3]. Lysins have emerged as antimicrobial agents owing to their potency and specificity for bacterial pathogens in comparison with antibiotics, which remain perpetually susceptible to bacterial resistance and may be ineffective in the presence of biofilms [4, 5]. Many lysins are species- or subspecies-specific, which means that they have a narrow spectrum of antimicrobial activity, and are only effective against bacteria from which they were produced [6]. Narrow targeting of bacterial pathogens represents a departure from many of the current approaches to treating infectious diseases, which often rely on broad-spectrum antibiotics that may be associated with off-target effects, which may be harmful to the host.

CF-301 (henceforth known as exebacase) has been identified as a promising lysin for research and development due to its specificity for Staphylococcus aureus, which is associated with substantial morbidity and mortality for both humans and animals [7]. Exebacase is the lead compound in this new class of antimicrobial agents and may ultimately serve to complement antibiotics in a variety of human syndromes [8, 9]. Exebacase’s relevance for veterinary medicine is outside of the scope of this manuscript and will not be discussed further.

2 Clinical Relevance
Exebacase, a first-in-class anti-staphyloccocal lysin, was found to be bacteriolytic against 250 S. aureus strains tested, including 120 methicillin-resistant S. aureus (MRSA)
isolates [10]. In time-kill studies, exebacase reduced S. aureus 1000-fold within half an hour, compared with 6–12 h required by antibiotics, suggesting a potential role in the treatment of human bloodstream infections.

Exebacase is an attractive agent for the treatment of S. aureus bacteremia because it acts synergistically with two key human blood factors, human serum lysozyme (HuLYZ) and human serum albumin (HSA), which normally have no nascent anti-staphylococcal activity [10]. Combinations of exebacase with two commonly used anti-staphylococcal antibiotics, vancomycin or daptomycin, yielded synergy in vitro and improved survival in staphylococcal-induced bacteremia in a murine model, suggesting combinations including exebacase and standard-of-care antibiotics could serve as an alternative strategy to treat S. aureus bacteremia, which continues to be associated with substantial morbidity and mortality in both immunocompetent and immunocompromised patients [8].

Recent work has established proof-of-principal. In a phase II, superiority design study, investigators randomly assigned 121 human volunteers with S. aureus bacteremia/ endocarditis to receive a single dose of exebacase or placebo in addition to standard-of-care antibiotics [11]. The primary efficacy endpoint was clinical outcome (responder rate) on day 14. Response rates on day 14 were 70.4% and 60.0% in the exebacase + antibiotics and antibiotics-alone groups, respectively (difference = 10.4, 90% confidence interval [CI] − 6.3 to 27.2; p = 0.31). Rates of adverse events were similar in both groups. Thirty-day all-cause mortality rates were 9.7% and 12.8% in the exebacase plus antibiotics and antibiotics-alone groups, respectively.

The most intriguing results were found in the subgroup analysis. For MRSA-infected patients, treatment with exebacase was associated with a marked reduction (21%) in the 30-day all-cause mortality, a 4-day reduction in median hospital length of stay, and a reduction in 30-day hospital readmission rates in MRSA-infected patients. Taken together, these findings suggest a potential role for exebacase in the treatment of bloodstream infections attributable to staphylococci, including MRSA; however, further studies are warranted to determine the optimal dose and duration of treatment.

Staphylococcus is among the most common causes of endovascular infections, including infective endocarditis (IE), which may occur in the setting of a bloodstream infection [12–14]. In an experimental aortic valve MRSA IE rabbit model, transthoracic echocardiography was utilized to evaluate the in vivo effect of exebacase on vegetation progression when combined with daptomycin (versus daptomycin alone) [8]. One dose of exebacase in addition to daptomycin cleared significantly more vegetation than daptomycin alone, and MRSA counts in the combination group were significantly lower than those of untreated controls (p < 0.0001) and the daptomycin-alone group (p < 0.0001). Findings from this animal model suggest that exebacase has potential applications to address staphylococcal bloodstream infections and infectious endocarditis, and further suggest that the agent may be useful for other types of infection.

### 2.1 Osteomyelitis

Bone infections with drug-resistant organisms also pose a therapeutic challenge [15, 16]. Patients are often subjected to prolonged courses of intravenous antimicrobial therapy (6–8 weeks) and treatment failure is not uncommon [17]. In this setting, exebacase has emerged as a promising addition to the standard of care for difficult-to-treat infections. In an acute MRSA osteomyelitis model, rats receiving no treatment or treatment with daptomycin, exebacase, or daptomycin plus exebacase had means of 5.13, 4.09, 4.65, and 3.57 log10 colony forming units (CFU)/g of bone, respectively [9]. All rats receiving treatment had a smaller bacterial burden than untreated animals (p ≤ 0.0001), with daptomycin plus exebacase being more active than daptomycin alone (p = 0.0042) or exebacase alone (p < 0.001).

Exebacase also has the potential to be used in patients with prosthetic joint infections due to staphylococci. For example, in patients with relapsing prosthetic knee infection, the only surgical option is exchange of the prosthesis [18, 19]; however, surgical exchange can be associated with loss of function and mortality [20–22]. In one small study, exebacase was used during arthroscopic knee debridement and implantation followed by suppressive tedizolid as salvage therapy in patients with prior prosthetic knee revisions complicated by relapsing knee infection [23]. Exebacase (75 mg/mL; 30 mL) was administered directly into the joint during arthroscopy. No adverse events occurred in the four patients who underwent the procedure; all patients received daptomycin 8 mg/kg and linezolid 600 mg twice daily (4–6 weeks) as primary therapy, followed by tedizolid 200 mg/day as suppressive therapy. After more than 1 year of follow-up, the clinical outcome was favorable in two patients with resolution of septic arthritis.

### 2.2 Biofilms

Biofilms are comprised of surface-associated microbial cells within an extracellular matrix [24]. This microenvironment represents a protected mode of growth that allows cells to survive in hostile environments and to withstand a variety of threats, including antimicrobial agents, and treatment failure is common [25, 26]. Biofilms form in a variety of human tissues, including bone, skin, cardiac tissue, and the upper respiratory, intestinal and urinary tracts [27]. Medical devices, such as intravenous catheters, prosthetic joints, and pacemakers, are frequent sites of biofilm formation and pose
a therapeutic challenge [28, 29]. Addressing biofilm-related infections is an unmet medical need [25, 30, 31].

In order to evaluate exebacase in this microenvironment, minimum biofilm-eradicating concentration (MBEC) assays were performed on *S. aureus* strains [32]. The effectiveness of exebacase was demonstrated against *S. aureus* biofilms formed on catheters, glass polystyrene, and surgical mesh. In catheters, exebacase removed all biofilm within 60 min and killed all released bacteria by 6 h. Mixed-species biofilms, formed by *S. aureus* and coagulase-negative *Staphylococcus* on several surfaces, were removed by exebacase and activity was greatly improved in combinations with the other agents, such as cell wall hydrolase lysostaphin.

A series of *in vitro* pharmacodynamic (PD) parameters, including the post-antibiotic effect (PAE), post-antibiotic sub-MIC effect (PA-SME), and sub-MIC effect (SME), were evaluated to determine how exebacase exposures impact the growth of staphylococci [33]. Mean PAE, PA-SME, and SME values up to 4.8, 9.3, and 9.8 h, respectively, were observed against 14 staphylococcal strains tested in human serum; a mouse thigh infection model demonstrated *in vivo* growth delays of more than 19 h, suggesting that reductions in bacterial fitness and virulence may substantially enhance exebacase efficacy.

Taken together, these studies indicate that exebacase is effective at treating a variety of staphylococcal *in vitro* and *in vivo* [7, 34–36]. Activity against other pathogens, such as *Streptococcus pyogenes*, *S. agalactiae*, and *S. dysgalactiae* remains strong but activity against other species is highly variable [34, 37–39]. Although human studies are limited, emerging data suggest that there may be a therapeutic role for exebacase in combination with existing antimicrobial therapy, with a clinical niche to address difficult-to-eradicate infections such as catheter-associated infections, endocarditis, prosthetic joint infections, and bacteremia due to staphylococci [8, 9, 40]. However, further studies are warranted to more fully categorize the safety and efficacy of this new agent in the treatment of biofilms, bone and joint infections, and endocarditis. For now, exebacase appears most promising for the treatment of staphylococcal bloodstream infections.

### 3 Future Directions

The challenge of antimicrobial drug resistance began soon after the discovery of the first antibiotics. Bacteria are continuously evolving to evade and withstand the commercially available antibiotics and novel treatment options are urgently needed. Bacteriophage-derived lysins are cell-wall hydrolytic enzymes that represent a new approach to address the expanding threat of antimicrobial resistance [6, 41, 42]. Exebacase is a recombinantly produced lysozyme that is rapidly bacteriocidal, eradicates biofilms, and has demonstrated clinical efficacy in combination with other antibiotics against a variety of staphylococcal pathogens that produce syndromes ranging from bacteremia to osteomyelitis. *In vitro* synergy for anti-biofilm activity of exebacase has been demonstrated with vancomycin, rifampin, and daptomycin against coagulase-negative *Staphylococci* (*S. epidermidis*) strains responsible for bone and joint infections of the knee, hip and shoulder. These data add to the existing evidence supporting the potential for exebacase to treat infections of prosthetic joints, although further studies are warranted. In the more immediate future, exebacase may serve as a novel treatment option for patients with bloodstream infections due to staphylococci. Recent work highlights the potential.

In October 2021, a phase II study was presented at IDWeek demonstrating that in patients with *S. aureus* bacteremia, exebacase used in addition to standard-of-care antibiotics resolved clinical symptoms more quickly than standard-of-care alone (3 days vs. 6 days) [oral presentation]. This randomized, double-blind, placebo-controlled study of 86 patients randomly assigned volunteers in a 2:1 ratio to a 2-h infusion of exebacase or placebo in addition to standard-of-care antibiotics. Among patients with MRSA bacteremia, the median time to symptom resolution was 3 days for those who received exebacase, compared with 7 days in patients who received standard-of-care alone. Patients with MRSA bacteremia showed greater symptom resolution (94.1%) than those treated with standard of care alone (81.8%).

Exebacase is a direct lytic agent now in phase III of clinical development. In addition to the attributes described above, exebacase has a minimal tendency for the development of resistance, no cross-resistance with antibiotics, and an extended *in vitro* and *in vivo* PAE. The agent is also active *in vitro* in pulmonary surfactant, suggesting a potential role in the treatment of bacterial pneumonia and other respiratory diseases for which treatment options remain scarce.

For example, severe disease during influenza infection may be the result of secondary bacterial pneumonia due to *S. aureus* [43, 44]. Viruses such as influenza A can disrupt physiological barriers and alter immunologic responses in humans, thereby altering the function of multi-protein inflammasomes, leading to increased susceptibility to staphylococci [45, 46]. The ability of staphylococcal pathogens to thrive under physiologic conditions is also associated with their capacity to form biofilms in the respiratory mucous membranes, rendering many antibiotics ineffective [47, 48]. Co-infection has been a major cause of mortality during influenza pandemics and better treatment options are urgently needed [49].

Nasal carriage of *S. aureus* is a risk factor for secondary staphylococcal pneumonia in influenza A virus-infected hosts. In a mouse model of lethal *S. aureus* lung infection,
exebacase was found to be efficacious alone and synergistic with daptomycin, potentially restoring the antimicrobial properties of an antibiotic that is known to become inactivated in the presence of pulmonary surfactant [37]. This approach may have particular relevance for patients with influenza pneumonia who subsequently develop staphylococcal pneumonia, which is associated with both acute and chronic lung injury as well as substantial mortality.

In the years ahead, exebacase may become an important addition to the therapeutic arsenal of agents used to treat invasive infections due to staphylococci, including bloodstream infections, endocarditis, lung infections, catheter-associated infections, and bone and prosthetic joint infections [9, 33, 36, 50]. Optimizing its use in clinical practice will be the focus of both basic and clinical research for years to come.

Declarations

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Conflicts of Interest Matthew W. McCarthy has no declarations to declare and reports no conflicts of interest. This work was conducted in compliance with international ethical standards.

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Author contributions Matthew W. McCarthy was responsible for all aspects of this manuscript.

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