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# CF-301 (Exebacase) and Daptomycin Treatment of Methicillin-Resistant *Staphylococcus aureus* Associated Experimental Osteomyelitis


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## Abstract


**Background:** Exebacase (CF-301), a bacteriophage-derived, recombinantly produced lytic enzyme, has been shown to be bactericidal against *S. aureus in vitro,* active in experimental animal models and is in a Phase 2 clinical study of *S. aureus* bacteremia including endocarditis. Staphylococcal osteomyelitis is difficult to treat with currently available antibiotics; Exebacase alone or in addition to traditional antibiotics, offers a potential strategy to treat this challenging infection type.

**Methods:** Osteomyelitis was established in 64 rats by bending the knee joint, inserting a 21G needle into the tibial process, and injecting 10 µl arachidonic acid and 50 µl of a ~$10^7$ colony forming unit (cfu) suspension of methicillin-resistant *S. aureus* (MRSA) IDRL-6169. One week after establishing infection, rats were randomly assigned to no treatment, daptomycin (60 mg/kg IP, twice daily, 4 days), Exebacase (40 mg/kg IV, single dose) or Exebacase plus daptomycin. Rats were sacrificed 4 days after the start of therapy and tibiae collected, weighed and cryopulverized for quantitative bacterial culture. Results were analyzed using the Kruskal-Wallis test and were reported as $\log_{10}$ cfu/gram of bone.

**Results:** Rats receiving no treatment had a mean (±SD) bacterial density of 5.13 (±0.34) $\log_{10}$ cfu/gram. Daptomycin, Exebacase and daptomycin plus Exebacase therapy groups had means (±SDs) of 4.09 (±0.37), 4.65 (±0.65) and 3.57 (±0.48) $\log_{10}$ cfu/gram, respectively (Figure). Compared to the untreated rats there were 1.04, 0.65 and 1.56 $\log_{10}$ cfu/gram reductions with daptomycin, Exebacase and the Exebacase plus daptomycin therapy, respectively. Colony counts in all treatment groups were significantly reduced compared to untreated rats (P≤0.0001). Daptomycin with Exebacase was more active than daptomycin (P=0.0042) or Exebacase (P <0.001) alone.

**Conclusions:** A single dose of Exebacase used in addition to daptomycin was the most active treatment tested in this rat model of MRSA osteomyelitis.


## Background

### Osteomyelitis

- Difficult to treat with high morbidity[1]
  - Irrigation and debridement
  - Long term antibiotic therapy
- Staphylococci are the most common organisms isolated [2]
  - Forms biofilms
  - Survive within osteoblasts
- Methicillin-resistant *Staphylococcus aureus* (MRSA) associated with poor patient outcomes[3]

### Lysins[4,5]

- Bacterial species-specific enzymes
- Hydrolyze the peptidoglycan in bacterial cell wall
- Does not require actively growing bacteria
- Acts immediately upon contact with bacterial cells

### Exebacase[4,5]

- Recombinantly produced lysin, derived within a *Streptococcus suis* prophage
- *S. aureus* specific bacteriolysis
- Rapidly bactericidal, shows minimal resistance development and has synergistic activity with vancomycin and daptomycin
- Penetrates bone
- Murine endocarditis model showed increased survival with one dose
- Recently completed phase 2 clinical trials for *S. aureus* bacteremia

## Methods

- Osteomyelitis was established in 64 male Sprague-Dawley rats

- Knee joint bent
- 21G needle inserted into the tibial process
- 10 µl arachidonic acid and 50 µl of a ~$10^7$ colony forming unit (cfu) suspension of MRSA IDRL-6169 injected

- One week after establishing infection, (day 8) rats were randomly assigned one of four treatment arms:
  - No treatment
  - Daptomycin (60 mg/kg, IP, twice daily, 4 days)
  - Exebacase (40 mg/kg, IV, single dose)
  - Exebacase plus daptomycin
- Rats were sacrificed 12 hours after the last dose of daptomycin (day 12)
- Tibiae collected, weighed and cryopulverized for quantitative bacterial culture
- Results analyzed using the Kruskal-Wallis test and reported as $\log_{10}$ cfu/gram of bone

## Results

- Mean bacterial load of untreated animals was 5.13 $\log_{10}$ cfu/gram of bone
- Bacterial load of all treatment groups was significantly reduced compared to untreated rats (P≤0.0001)
- Daptomycin plus Exebacase had significantly lower bacterial loads than animals treated with daptomycin (P=0.0042) or Exebacase (P<0.0001) alone

**Table. Reduction of bacterial load compared to untreated animals**

| Treatment Group | Reduction ($\log_{10}$ cfu/ gram) |
|---|---|
| **Daptomycin** | **1.04** |
| **Exebacase** | **0.65** |
| **Daptomycin and Exebacase** | **1.56** |

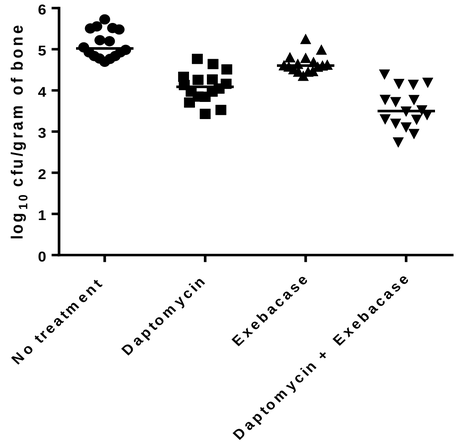


**Figure. Bacterial load of tibia ($\log_{10}$ cfu/gram of bone)**

## Conclusions

While treatment with daptomycin or exebacase alone showed a reduction in infection, exebacase in addition to daptomycin was more active and may offer a treatment for osteomyelitis.

## References


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