Evaluation of long-term outcomes in patients with osteomyelitis treated with a daptomycin-containing regimen
L Balter, B Donovan, K Lamp, D North, L Friedrich

Citation

Abstract
Objectives: Daptomycin is often used to treat patients with osteomyelitis. In this review, we describe the use of daptomycin for osteomyelitis. Material and methods: Inclusion criteria included patients ≥18 years, receipt of ≥2 weeks of daptomycin, and ≥6 months of follow-up. Outcomes and adverse events (AEs) were determined at end of therapy (EOT) and follow-up. Results: For this study, 29 patients met the inclusion criteria. A successful outcome was achieved in 86% of patients at EOT and 69% at follow-up. Conclusions: The most common pathogen was methicillin-resistant Staphylococcus aureus. The median daptomycin dosage was 4.2 mg/kg/day (3.5–7.1), and the median duration of therapy was 42 days (18–63). In all, 18 AEs were attributed to daptomycin in 9 patients; most were mild to moderate in severity. In a heavily pretreated cohort of patients, including those with prosthetic devices, daptomycin appeared to be effective for the treatment of osteomyelitis.

DISCLOSURES
This study was sponsored by Cubist Pharmaceuticals, Inc., Lexington, MA.

PROPRIETARY STATEMENT
B.J.D., K.C.L., D.S.N., and L.V.F. are employees of and shareholders in Cubist Pharmaceuticals, Inc. L.B. received research funding for this project and travel support from Cubist Pharmaceuticals, Inc. to present these data.

INSTITUTIONAL REVIEW BOARD APPROVAL
Using the US Department of Health and Human Services regulations found at 45 CFR 46.101 as a model, a central institutional review board (IRB) determined that this study was exempt from IRB review and oversight.

BACKGROUND
Osteomyelitis is difficult to treat, requiring prolonged treatment with intravenous and/or oral antibiotics. The risk of recurrence is high and can lead to reduced limb function, amputation, or death. Staphylococcus aureus is the most common pathogen. Vancomycin has been the drug of choice for the treatment of osteomyelitis due to methicillin-resistant S aureus (MRSA). However, recent literature suggests reduced efficacy of this agent, especially for infections caused by S aureus with a minimum inhibitory concentration (MIC) ≥2 μg/mL.

In animal models of MRSA osteomyelitis, daptomycin has been shown to be as effective as vancomycin or clindamycin. Limited data exist about the efficacy and safety of daptomycin in patients with osteomyelitis. In case reports and small case series with limited follow-up, daptomycin appeared to be effective in patients with osteomyelitis. The objective of this study was to describe the use of daptomycin in patients with osteomyelitis.

MATERIAL AND METHODS
A retrospective chart review was conducted in the United States from October 2005 through April 2006 from sites in Washington, DC, Orlando, FL, Charleston, SC, Denver, CO, Indianapolis, IN, and Munster, IN. Site investigators identified medical records of patients with osteomyelitis who had been treated with daptomycin and had follow-up for at least 6 months from the conclusion of therapy.

Patients ≥18 years of age were eligible for inclusion if they were diagnosed with osteomyelitis by culture, radiography, histopathology, or clinical presentation, and had received at least 2 weeks of daptomycin therapy. Patients were excluded if they received daptomycin as part of a clinical trial or if
their clinical outcomes had been previously presented or published. A standardized case report form (CRF) was used to capture data relevant to the diagnosis and management of osteomyelitis.

Bacterial cultures obtained within 6 weeks before and up to 2 days after the initiation of daptomycin were included in the analysis. Concomitant use of other antibiotics with daptomycin also was recorded. If the patient record indicated the use of other antibiotics for the treatment of osteomyelitis prior to daptomycin, the antibiotics used and the reasons for discontinuation were recorded.

Clinical outcomes, as assessed by the investigator at each study site, were evaluated at the end of therapy (EOT) with daptomycin and at follow-up using the definitions for cure, improved, failure, and clinical success that have been published previously. If daptomycin was discontinued because of an adverse event (AE), the patient was considered a failure at both EOT and at follow-up.

Investigators recorded and assessed AEs for their relationship to daptomycin and for their severity. Any action taken in response to the AE also was recorded. An additional review of each CRF was conducted by the sponsor to ensure capture of all AEs.

All data are listed as median (minimum, maximum). Outcome comparisons of interest were performed by the chi-square method. A paired t test was used to analyze erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) data. The level of statistical significance for all tests was set at <0.05.

RESULTS

A total of 34 CRFs from 6 sites were submitted. Five patients from 4 sites did not meet the inclusion criteria, primarily because of inadequate follow-up. The remaining 29 patients from 4 sites are described in this report. The exact date of the follow-up visit was not available for 5 patients; however, the month and year were provided. For these patients, the first day of the follow-up month was used. Although the minimum follow-up period was defined a priori to be at least 6 months, 2 patients had follow-up assessments within the 14 days preceding that period and were included in this analysis.

Twenty-eight patients satisfied at least 2 of the criteria for diagnosis of osteomyelitis (culture, radiography, histopathology, or clinical presentation); 1 patient had only a magnetic resonance image (MRI) indicating osteomyelitis.

Select demographic information and infection details can be found in Table 1.

Table 1: Demographics and infection details (n=29)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years, mean = SD)</td>
<td>54.2 ± 14.3</td>
</tr>
<tr>
<td>Gender</td>
<td>Female</td>
</tr>
<tr>
<td>Weight (kg, mean = SD)</td>
<td>89.7 ± 23.4</td>
</tr>
<tr>
<td>Creatinine clearance (mL/min)</td>
<td>27 (9.1)</td>
</tr>
<tr>
<td>Anatomic location of osteomyelitis</td>
<td></td>
</tr>
<tr>
<td>Lower extremity</td>
<td>13 (44.8)</td>
</tr>
<tr>
<td>Upper extremity</td>
<td>7 (24.1)</td>
</tr>
<tr>
<td>Vertebral</td>
<td>6 (20.7)</td>
</tr>
<tr>
<td>Sternum/chest wall</td>
<td>3 (10.5)</td>
</tr>
<tr>
<td>Type of osteomyelitis</td>
<td></td>
</tr>
<tr>
<td>Prosthetic material</td>
<td>12 (41.4)</td>
</tr>
<tr>
<td>Contiguous (nondiabetic)</td>
<td>11 (37.9)</td>
</tr>
<tr>
<td>Contiguous (diabetic)</td>
<td>4 (13.8)</td>
</tr>
<tr>
<td>Hematogenous</td>
<td>2 (6.9)</td>
</tr>
</tbody>
</table>

The most common anatomic location of osteomyelitis was the lower extremity, and fewer than half the patients had osteomyelitis associated with prosthetic material. Twenty-eight patients (97%) had 1 or more risk factors for osteomyelitis: the most common were prior surgery at the site of infection (n=15, 52%) and peripheral vascular disease (n=3, 10%). Twenty-four percent of patients had diabetes.

Twenty-three patients (79%) had a documented positive culture within 6 weeks before initiation of daptomycin therapy. Culture sources included bone (34%), deep tissue - not otherwise specified (17%), synovial fluid/synovium (17%), knee effusion, deep surgical wound, and sinus tract (3% each). Among the 6 patients with a negative culture or no culture documented, 1 patient was being treated for a relapse; previous bone culture grew Enterococcus faecalis, Peptococcus species, and gram-positive bacilli. The median time between obtaining a culture and starting daptomycin was 6 days (0–36). Of the 5 patients with deep tissue cultures, all had documented surgical evidence of osteomyelitis. Isolated pathogens are shown in Table 2; MRSA was most common.
During the 6 months prior to receiving daptomycin, 22 patients (76%) received an antibiotic for the treatment of osteomyelitis; of these, 16 (73%) received vancomycin. In the patients receiving vancomycin, 10 (63%) discontinued therapy because of allergy or toxicity, while 3 (19%) were considered vancomycin failures. In the 4 weeks immediately before receiving daptomycin, 15 of the 29 total patients (52%) received an antibiotic for >24 hours, most commonly vancomycin (67%). One patient received linezolid. The median duration of therapy in the 4 weeks before the initiation of daptomycin was 17 days (4–34).

The principal reasons for initiating daptomycin were failure of previous antibiotic therapy (n=13, 45%) and intolerance to a previous antibiotic (n=9, 31%). Five patients (17%) received daptomycin as initial therapy. The remaining 2 patients received daptomycin for reasons unrelated to prior antibiotic failure or intolerance. The median dose of daptomycin was 4.2 mg/kg (3.5–7.1); 5 patients (17%) received a dose ≥6 mg/kg. Twenty-seven patients (93%) received daptomycin once daily; the regimen was modified to once every 48 hours in the 2 patients with a creatinine clearance <30 mL/min. The median duration of therapy was 42 days (18–63).

Fourteen patients (48%) received concomitant antibiotic therapy with daptomycin. Rifampin was most common, used in 5 patients (17%), including 3 of 12 patients with prosthetic material. The 9 remaining patients received agents that are commonly used to treat infections caused by gram-negative pathogens (eg, ciprofloxacin).

The median time from EOT to follow-up assessment was 9 months (6–18). Forty-eight percent and 17% of patients had their follow-up assessment performed at least 9 and 12 months, respectively, after discontinuing daptomycin therapy.

Clinical outcomes are presented in Figure 1. The success rate was 86% at EOT and 69% at follow-up. Of the 4 failures at EOT, 3 were due to AEs. These patients were considered clinically improved by the site investigator when daptomycin was discontinued. Of the 9 failures identified at follow-up, 5 had been classified as cures at EOT.

Among patients with prosthetic material (n=12), the clinical success rates at EOT and follow-up were 83% (10/12) and 67% (8/12), respectively. Six of these patients had their prosthetic material removed during daptomycin therapy or within 2 weeks before starting daptomycin; however, the exact reason for removal was not collected.

The following factors did not have a statistically significant effect on outcome at EOT or follow-up: daptomycin dose ≥6 mg/kg/dose; duration of daptomycin therapy >28 days; receipt of daptomycin monotherapy; use of concomitant rifampin; receipt of any antibiotic therapy in the 4 weeks before receiving daptomycin; debridement within 2 weeks of starting daptomycin (patients without prosthetic material); removal of prosthetic material during therapy with daptomycin or within 2 weeks prior to starting daptomycin.

Seven patients (24%) received a potentially effective antibiotic after daptomycin therapy concluded. Four were considered improved at EOT; each was switched to an oral antibiotic (linezolid [n=3] or dicloxacillin [n=1]) for continued treatment. Three were considered failures because of an AE while on daptomycin, and the remaining patient received concomitant ertapenem that continued for 12 days beyond the end of daptomycin therapy.

The data from all patients with a negative culture or with no culture documented within the specified timeframe were closely reviewed. All 6 of the patients exhibited a clinical success at EOT, and 5 at follow-up (median [min, max]
number of months to follow-up was 8.2 months [6–12]). All 6 of these patients had either radiologic (n=3), histopathologic (n=2), or both (n=1) criteria supporting the diagnosis of osteomyelitis.

Erythrocyte sedimentation rate and CRP serum concentrations were not monitored in all cases; however, baseline and follow-up data were available for 21 and 18 patients, respectively. Mean ESR values declined significantly during therapy with daptomycin (from 57.6 ± 45.2 mm/h to 28.0 ± 30.6 mm/h; P <0.001). Similarly, mean CRP values also declined over time, but were not found to be statistically significant (from 27.4 ± 56.08 mg/dL to 4.7 ± 6.87 mg/dL; P=0.100). This may be explained by the presence of an unusually high CRP value at baseline for 1 patient.

Eighteen AEs were deemed possibly or probably related to daptomycin in 9 patients; 12 were considered serious. Seven (39%) AEs were considered mild, 8 (44%) were moderate, and 3 (17%) were severe. Daptomycin was discontinued in 1 patient each because of myalgia, rhabdomyolysis, or papilledema. At the end of data collection, 15 (83%) AEs resolved; however, in 2 different patients papilledema with blurred vision and arthralgia had not.

The patient who developed papilledema was a 41-year-old female with MRSA osteomyelitis. She was treated with daptomycin 3.6 mg/kg once daily. On Day 23, she was admitted to the hospital with a complaint of visual problems (difficulty focusing); daptomycin was discontinued. Fundoscopy revealed papilledema of unclear etiology; a computed tomography (CT) scan of her head was normal. The patient was treated with acetazolamide, and her symptoms improved significantly. However, after 7 months of follow-up, her vision had not completely returned to baseline. No follow-up information beyond 7 months was available. The investigator considered this AE to be moderate in severity and possibly related to daptomycin.

The patient who developed rhabdomyolysis was a 65-year-old female with MRSA osteomyelitis. She received daptomycin 7.1 mg/kg once daily. After 19 days, she developed myalgias and her dose was reduced to 3.6 mg/kg. She received the lower dose for 3 days, but her symptoms continued, so daptomycin was discontinued after 22 days. At baseline, her creatine phosphokinase (CPK) level was 31 U/L. After Days 9, 15, and 21, her CPK levels were 857, 2,750, and 1,056 U/L, respectively. Her serum creatinine at baseline was 0.6 mg/dL and was 1.0, 0.8, 0.8, and 0.8 mg/dL on Days 9, 15, 21, and 29, respectively. No information regarding urine myoglobin or CPK isoenzymes was available. The patient’s symptoms resolved 7 days after daptomycin was discontinued. No CPK value was reported after Day 21. The investigator considered this AE to be moderate in severity and probably related to daptomycin.

Of 26 patients who had CPK levels documented while on daptomycin, 5 (19.2%) had values >200 U/L during treatment with daptomycin and 2 had a value >500 U/L. Among the patients with a CPK value >200 U/L, the median (min, max) baseline value was 159 U/L (26–342) and increased to a median (min, max) of 347 U/L (285–2,750).

DISCUSSION

This report describes the long-term outcomes of daptomycin treatment in patients with osteomyelitis. The rate of clinical success was high at EOT and decreased at follow-up, including in patients with osteomyelitis associated with prosthetic material. Response to daptomycin therapy was further supported by the decreases seen for both ESR and CRP, markers commonly used to assess response to therapy. These results support the findings of other investigators who have described the efficacy of daptomycin in bone and joint infections. AEs attributed to daptomycin were primarily mild to moderate in severity. Although the correct daptomycin dose for the treatment of osteomyelitis is unknown, the median dose reported here is lower than the dose approved for the treatment of osteomyelitis.

This study does have limitations, including its retrospective, noncomparative design. As a result, there was a lack of a priori criteria for the diagnosis of osteomyelitis; however, the inclusion criteria required microbiologic, histopathologic, radiologic, and/or clinical evidence to support the diagnosis. Surgical interventions were not controlled for and the sample size was small.

The current recommendation for the treatment of osteomyelitis is 4–6 weeks of antibiotic therapy. Several antibiotics may be used to treat osteomyelitis, but vancomycin remains the antibiotic of choice for therapy. However, clinical failures associated with reduced susceptibility to vancomycin among isolates of S aureus have been reported in patients with osteomyelitis. This underscores the need for alternative therapies.
CONCLUSION
In a heavily pretreated cohort of patients, including those with prosthetic devices, daptomycin treatment resulted in successful clinical outcomes in the treatment of patients with osteomyelitis due to gram-positive pathogens, including MRSA. Most patients maintained positive outcomes at least 6 months after daptomycin therapy was completed. These data should be confirmed in randomized, controlled clinical trials.

ACKNOWLEDGEMENTS
These data were presented at the 44th Annual Meeting of the Infectious Diseases Society of America, Toronto, Ontario, Canada, 2006. Poster #208. Infectious Diseases Society of America, Alexandria, Virginia.

The authors would like to thank Nayiri Baljian for her tireless efforts managing this study, Patricia Bernardo, MD, for the statistical analysis of ESR and CRP data, and Jeff Kuper, PharmD, from PharmaWrite, LLC, for his assistance with manuscript preparation.

References
Author Information

Laurence Balter, MD
Kane and Davis Associates

Brian J. Donovan, PharmD
Cubist Pharmaceuticals, Inc.

Kenneth C. Lamp, PharmD
Cubist Pharmaceuticals, Inc.

Donald S. North, PharmD
Cubist Pharmaceuticals, Inc.

Lawrence V. Friedrich, PharmD
Cubist Pharmaceuticals, Inc.