Randomized Controlled Trial of the Safety and Efficacy of Daptomycin versus Standard-of-Care Therapy for Management of Patients with Osteomyelitis Associated with Prosthetic Devices Undergoing Two-Stage Revision Arthroplasty

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The prevalence of *Staphylococcus aureus* causing prosthetic joint infection (PJI) supports investigation of higher doses of daptomycin in the management of PJI. This was a prospective, randomized controlled trial studying safety and efficacy of daptomycin (6 and 8 mg/kg of body weight) compared with standard-of-care therapy for PJI. This open-label study randomized 75 patients undergoing 2-stage revision arthroplasty to daptomycin at 6 or 8 mg/kg or a comparator (vancomycin, teicoplanin, or semisynthetic penicillin). After prosthesis removal, patients received 6 weeks of antibiotic treatment and a 2- to 6-week antibiotic-free period before implantation of a new prosthesis. Test of cure (TOC) was within 1 to 2 weeks after reimplantation. The primary objective was evaluation of creatine phosphokinase (CPK) levels. Secondary objectives were clinical efficacy and microbiological assessments. Of 73 CPK safety population patients, CPK elevation of >500 U/liter occurred in 4 of 25 (16.0%) (daptomycin, 6 mg/kg) and 5 of 23 (21.7%) (daptomycin, 8 mg/kg) daptomycin-treated patients and 2 of 25 (8.0%) comparator patients. Adverse-event rates were similar among daptomycin and comparator groups. Among modified intent-to-treat patients at TOC, clinical success rates were 14 of 24 (58.3%) for 6 mg/kg daptomycin, 14 of 23 (60.9%) for 8 mg/kg daptomycin, and 8 of 21 (38.1%) for the comparator. Overall microbiological success at TOC was 12 of 24 (50.0%) for 6 mg/kg daptomycin, 12 of 23 (52.2%) for 8 mg/kg daptomycin, and 8 of 21 (38.1%) for comparator patients. In conclusion, daptomycin at 6 and 8 mg/kg given for up to 6 weeks was safe and appeared to be effective in managing staphylococcal PJI using a 2-stage revision arthroplasty technique in a total of 49 patients.

Prosthetic joint infection (PJI) occurs in 0.5% to 1.0% and 0.5% to 2% of hip and knee replacements, respectively (5, 20, 24, 25). PJI is predominantly caused by *Staphylococcus aureus* (28%) and coagulase-negative staphylococci (CoNS) (25%) (23). PJI is associated with mortality (up to 2.5%) and significant morbidity, and outcomes are poor (8). There are no prospective, randomized controlled trials to guide treatment in this area (16, 21). Conducting trials is challenging due to the difficulty of identifying patients and confounding outcomes by prior use of antibiotics.

The ideal antimicrobial agent should be bactericidal, with activity against biofilm-producing microorganisms (26). Daptomycin exhibits rapid, concentration-dependent bactericidal activity *in vitro* against Gram-positive organisms, including *S. aureus* (regardless of methicillin susceptibility), *Staphylococcus haemolyticus*, and *Staphylococcus epidermidis* (4). Clinical outcomes in osteomyelitis from a retrospective, noncomparative registry showed that daptomycin doses of >4 mg/kg of body weight were more effective than doses of ≤4 mg/kg (88% versus 65%; *P* = 0.013) (15).

This study assessed the safety and efficacy of 6 and 8 mg/kg daptomycin compared with standard-of-care therapy in patients with hip or knee PJI caused by methicillin-resistant *S. aureus* (MRSA), methicillin-susceptible *S. aureus* (MSSA), or CoNS. Patients undergoing 2-stage procedures were evaluated to permit collection of microbiological samples before and after treatment.

MATERIALS AND METHODS

Study population. The population was aged 18 years and over, with a confirmed hip or knee PJI that had no previous revision for infection and for which the patient was expected to undergo a 2-stage revision arthroplasty. Patients were required to have 2 cultures positive for staphylococci from surgical specimens, blood culture, or joint aspiration fluid at baseline. In the event that intraoperative cultures were negative or pending, patients could be enrolled based on Gram stain or histopathological evidence of Gram-positive pathogens. There were no restrictions on prior antibiotic therapy. Patients with severe renal impairment (creatinine clearance < 30 ml/min) as estimated by the Cockcroft-Gault equation were excluded. Patients with infecting organisms other than staphylococci were also excluded.

Study design and treatments. This was a prospective, randomized, open-label study in 22 centers in the United States, the United Kingdom, and Russia from June 2007 through June 2010 and was conducted in

Received 6 January 2012 Returned for modification 4 May 2012

Accepted 12 August 2012

Published ahead of print 20 August 2012

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doi:10.1128/AAC.00038-12

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accordance with the ethical principles originating in the Declaration of Helsinki and its amendments, consistent with good clinical practices and local regulatory requirements. The study was approved by independent institutional review boards at each site. Written informed consent was obtained before any study-specific procedures.

Anti-infective drugs with no known activity against the organism infecting the prosthesis were permitted to treat a defined but unrelated infection. Baseline cultures positive for *S. aureus*, taken at surgery number 1, were mandated for randomization into the study; the use of antibiotics prior to surgery number 1, therefore, would not confound clinical efficacy. In addition, perioperative antibiotics (up to 72 h postoperatively) and beads or cement impregnated with vancomycin, gentamicin, or tobramycin were permitted. It was determined that perioperative antibiotics administered between surgery number 1 and confirmed positive cultures within 3 to 5 days would also not confound the clinical outcome given the treatment modality of PJI with average treatment duration of 6 weeks.

Randomization was stratified by the anatomical location of the infected joint (hip or knee) and degree of renal function (30 to <50 ml/min or ≥ 50 ml/min). Patients randomized to intravenous daptomycin received 6 mg/kg or 8 mg/kg as a 30-min infusion every 24 h. Patients randomized to standard of care received intravenous therapy with either vancomycin at 1 g every 12 h over 60 to 100 min (with institutional adjustment per pharmacokinetics), teicoplanin at 6 mg/kg every 24 h over 30 min (or according to local standard of care), or a semisynthetic penicillin (SSP) administered according to standard of care. After an end-of-therapy (EOT) evaluation, there was an antibiotic-free period of 2 to 6 weeks, followed by implantation of a new prosthesis. Perioperative antibiotics were again permitted. Efficacy was evaluated at the test-of-cure (TOC) visit (at hospital discharge or within 2 weeks after reimplantation if still hospitalized). The timing for the TOC visit was chosen based on standard of care where clinical efficacy assessments are performed 2 weeks after reimplantation. Patients with a successful outcome at TOC were evaluated at a follow-up visit 3 to 4 months after reimplantation.

Safety evaluations. The primary safety endpoint, creatine phosphokinase (CPK; elevation above 500 U/liter), was evaluated from day 3 of study drug administration to 7 days after the last dose. CPK monitoring was performed as per the current Cubicin (daptomycin for injection) prescribing information (7). All patients were monitored for the development of muscle pain or weakness. Patients who developed unexplained elevations in CPK were monitored more frequently. In patients with unexplained signs and symptoms of myopathy in conjunction with CPK elevation of $>1,000$ U/liter ($\sim 5\times$ upper limit of normal [ULN]) or in patients without reported symptoms who had marked elevations in CPK, $>2,000$ U/liter ($\geq 10\times$ ULN), study drug administration was discontinued. If a patient experienced a CPK level of $>1,000$ U/liter, isoenzymes and serum and urinary myoglobin were also checked at that time, and CPK was checked daily until the results were within the normal range. Other safety parameters were assessed throughout the study, including adverse events (AEs), serious AEs (SAEs), treatment-emergent AEs (TEAEs), laboratory assays, vital signs, concomitant medications, and physical examinations. An AE was defined as any untoward medical occurrence in a patient administered the study medication, not necessarily having a causal relationship with the treatment. An SAE was an AE that occurred at any dose resulting in either death, a life-threatening event, inpatient hospitalization, or prolongation of existing hospitalization, a persistent or significant disability, a congenital anomaly, or an important medical event that may not result in death, be life-threatening, or require hospitalization but can jeopardize a patient's health or well-being and may require medical or surgical intervention. A TEAE was defined as an AE that occurred after the start of the first dose of study medication.

Clinical and microbiological evaluations. Clinical and microbiological responses were determined at TOC. Patients were classified as show-

ing success (resolution or improvement of baseline clinical and radiological findings and negative cultures), being nonevaluable (not seen at TOC), or showing failure (no improvement or worsening at TOC or withdrawal for an unsatisfactory response or AE). Microbiology (surgical specimens and blood cultures) was assessed at baseline, at reimplantation, and at the discretion of the investigator. Microbiological success was defined as eradication of all baseline pathogen(s) with no evidence of superinfection between reimplantation and TOC and no synovial cultures between EOT and TOC that were positive for a baseline pathogen. Microbiological failure was the presence of a persisting or superinfecting Gram-positive pathogen between EOT and TOC or a positive Gram stain from reimplantation for patients who were culture negative at baseline and enrolled based on the presence of Gram-positive cocci on stain. Patients were nonevaluable if they had no cultures taken at reimplantation.

Statistical analysis. A total of 72 patients were targeted for enrollment. The study was not powered to detect statistical differences or to demonstrate noninferiority among treatments. However, with a sample size of 24 evaluable patients per treatment group, there was a 92% chance of seeing at least one occurrence of elevated CPK with a true rate of 10%. Descriptive statistics (sample size [n], mean, standard deviation [SD], median, minimum, and maximum) were presented for continuous data. For categorical data, frequency and percentage of each category were presented unless specified otherwise. The CPK safety population consisted of patients with at least 3 days of study drug treatment and CPK values. The safety population included any patient receiving study drug. The efficacy populations for analysis were the intent-to-treat (ITT) (all patients receiving study drug) and the mITT (ITT patients with at least 1 staphylococcal baseline pathogen) populations. The primary safety endpoint was the occurrence of elevated CPK (>500 U/liter) in the CPK safety population. An additional safety analysis assessed sustained CPK elevations (2 consecutive evaluations with CPK of >500 U/liter). Secondary safety endpoints included AEs and laboratory parameters. Secondary endpoints related to efficacy included clinical outcome, microbiological response, and overall response (clinical and microbiological response).

RESULTS

Patient disposition and analysis populations. Seventy-five patients were randomized (Fig. 1). Among 25 patients randomized to a comparator, 23 received vancomycin, 1 received teicoplanin, and 1 received an SSP. One patient withdrew prior to comparator treatment. Across all 3 groups, 6 patients did not meet microbiological criteria and were excluded from the mITT population. Fifty-three patients completed TOC, with 42 of these assessed at follow-up. Reasons for nonevaluability and early discontinuations are listed in Fig. 1. The proportions of patients excluded for the cited reasons were similar among treatment groups.

Patient demographics and baseline characteristics. Baseline characteristics are summarized in Table 1, and all treatment groups showed similar demographic characteristics. MSSA was the predominant baseline infecting pathogen. There were fewer MRSA infections in the daptomycin 6-mg/kg group (3/25 [12.5%]) and comparator group (3/25 [14.3%]) than in the daptomycin 8-mg/kg group (7/24 [30.4%]). CoNS infections were equally distributed across groups. The median duration of treatment in both daptomycin treatment groups was 42 days, and that in the comparator group was 40 days.

Primary outcome. More patients in the daptomycin 6- and 8-mg/kg groups (4/25 [16.0%] and 5/23 [21.7%], respectively) had CPK of >500 U/liter than in the comparator group (2/25 [8.0%]). The differences were not statistically significant. Two patients treated with daptomycin had CPK values of $>1,000$ U/liter (assessed as rhabdomyolysis by investigator). One patient in the

FIG 1 Patient enrollment and reasons for early discontinuations. The safety population was comprised of any patient who received any amount of study medication. The ITT population was comprised of all patients who were randomized and received any amount of study medication. The CPK safety population was comprised of patients who received a minimum of 3 days of dosing with study drug, had a baseline CPK value, and had a minimum of 1 post baseline CPK assessment as assessed by the central laboratory between day 3 of study drug administration through 7 days after the last dose of study drug. The mITT population was comprised of patients in the ITT population who had at least 1 staphylococcal baseline infecting pathogen. The TOC was defined as the time of hospital discharge or within 1 to 2 weeks after reimplantation if the patient remained hospitalized. The follow-up visit was a visit on which patients who were considered a success at TOC were clinically assessed 3 to 4 months after reimplantation. One patient randomized to the comparator group withdrew prior to receiving study treatment.

6-mg/kg group with a history of fibromyalgia, obesity, and treatment with fenofibrate had a CPK of 7,211 U/liter on day 11, associated with muscle pain, elevated serum myoglobin, and normal renal function. Four days after stopping daptomycin, CPK was normal and symptoms had resolved. The second patient (in the 8-mg/kg group) had a CPK of 1,220 U/liter on day 15, with a peak of 3,471 U/liter the following day and elevated serum myoglobin. Daptomycin was withdrawn, and the patient was admitted to the hospital for intravenous fluids. Three days later, CPK was normal. There were no symptoms of myopathy. Sustained elevations of CPK of >500 U/liter (>2 consecutive values) occurred in 5 patients: 2 in the daptomycin 6-mg/kg group and 3 in the daptomycin 8-mg/kg group.

Safety. A summary of AEs, SAEs, and study drug discontinuations is presented in Table 2. There were no differences in the incidence of any SAE across groups. No deaths occurred in the study.

AEs led to discontinuation in 2 of 25 (8.0%), 4 of 24 (16.7%), and 4 of 25 (16.0%) patients in the daptomycin 6- and 8-mg/kg and comparator groups, respectively. These events in the dapto-

mycin 6-mg/kg group were rash (possibly related to treatment) and rhabdomyolysis (related to treatment). In the daptomycin 8-mg/kg group, events were increases in CPK (in 2 patients, related to treatment), rhabdomyolysis (related to treatment), and endocarditis (unrelated to treatment). In the comparator group, events were renal failure (unrelated to treatment) and urinary tract infection, pulmonary embolism, and drug hypersensitivity (all related to treatment). The overall incidences of TEAEs were 23 of 25 (92.0%), 19 of 24 (79.2%), and 22 of 25 (88.0%) patients in the daptomycin 6-mg/kg, daptomycin 8-mg/kg, and comparator groups, respectively. The most commonly reported TEAEs are summarized in Table 3. The majority of TEAEs were unrelated to study treatment.

Clinical efficacy. Clinical success rates for the mITT population at TOC were 14 of 24 (58.3%) and 14 of 23 (60.9%) in the daptomycin 6- and 8-mg/kg groups, respectively, and 8 of 21 (38.1%) in the comparator group. Table 4 compares outcomes at TOC across groups. The most common reasons for failures were

TABLE 1 Selected demographic and baseline characteristics of the safety/ITT population

Characteristic ^a	Daptomycin		Comparator (n = 25)
	6 mg/kg (n = 25)	8 mg/kg (n = 24)	
Age (yrs)			
Mean (SD)	63.5 (13.3)	60.4 (13.2)	61.2 (12.7)
Range	32–81	37–85	30–82
Gender, n (%)			
Female	14 (56.0)	10 (41.7)	11 (44.0)
Male	11 (44.0)	14 (58.3)	14 (56.0)
Race, n (%)			
White	24 (96.0)	24 (100.0)	25 (100.0)
Black or African American	1 (4.0)	0	0
BMI (kg/m ²)			
Mean (SD)	30.6 (8.8)	29.5 (7.0)	31.1 (8.0)
Range	19.3–54.2	19.5–43.8	20.0–55.6
Site of infection, n (%)			
Hip	10 (40.0)	11 (45.8)	10 (40.0)
Knee	15 (60.0)	13 (54.2)	15 (60.0)
Risk factors, n (%)			
Prior surgery on joint	10 (40.0)	9 (39.1)	10 (40.0)
Prior infection of joint or bone	7 (29.2)	6 (26.1)	7 (28.0)
Complicated initial surgery	5 (20.0)	5 (21.7)	2 (8.0)
Diabetes	5 (20.0)	5 (21.7)	5 (20.0)
Baseline infecting pathogen, n (%)			
<i>S. aureus</i>	24 (96.0)	23 (95.8)	21 (84.0)
MRSA	14 (58.3)	14 (60.9)	10 (47.6)
MSSA	3 (12.5)	7 (30.4)	3 (14.3)
CoNS	11 (45.8)	7 (30.4)	7 (33.3)
MRCoNS	8 (33.3)	9 (39.1)	7 (33.3)
MSCoNS	6 (25.0)	5 (21.7)	6 (28.6)
Unknown methicillin susceptibility ^b	1 (4.2)	1 (4.3)	1 (4.8)
Unknown methicillin susceptibility ^b	1 (4.2)	3 (13.0)	0
Mixed staphylococcal infection ^c	2 (8.3)	0	4 (19.0)

^a BMI, body mass index; MRCoNS, methicillin-resistant coagulase-negative staphylococci; MSCoNS, methicillin-susceptible coagulase-negative staphylococci.

^b No methicillin testing performed.

^c Mixed *S. aureus* and CoNS.

microbiological failure at TOC or discontinuation due to an AE. Two patients (both in the daptomycin 6-mg/kg group) failed due to an unsatisfactory response; debridement and aspiration were required for 1 patient, while wound revision for infection was

TABLE 2 Summary of AEs and discontinuations (safety population)

AE	No. (%) treated with daptomycin at:		No. (%) treated with comparator
	6 mg/kg (n = 25)	8 mg/kg (n = 24)	
Patients with at least one:			
SAE	8 (32.0)	4 (16.7)	8 (32.0)
Drug-related SAE	2 (8.0)	2 (8.3)	1 (4.0)
AE causing death	0	0	0
AE causing discontinuation of study drug	2 (8.0)	4 (16.7)	4 (16.0)
Drug-related AE causing discontinuation	2 (8.0)	3 (12.5)	2 (8.0)
CPK increase causing discontinuation	1 (4.0)	3 (12.5)	0
AE classified as rhabdomyolysis causing discontinuation	1 (4.0)	1 (4.2)	0

TABLE 3 TEAEs reported in 10% or more of patients in any treatment group

TEAE	No. (%) treated with daptomycin		No. (%) treated with comparator
	6 mg/kg (n = 25)	8 mg/kg (n = 24)	
Any TEAE	23 (92.0)	19 (79.2)	22 (88.0)
Drug-related AE	6 (24.0)	7 (29.2)	9 (36.0)
Infections	9 (36.0)	10 (41.7)	11 (44.0)
Urinary tract infection	4 (16.0)	1 (4.2)	4 (16.0)
Gastrointestinal	11 (44.0)	7 (29.2)	7 (28.0)
Nausea	5 (20.0)	3 (12.5)	4 (16.0)
Constipation	4 (16.0)	2 (8.3)	1 (4.0)
General disorders	8 (32.0)	4 (16.7)	11 (44.0)
Pyrexia	4 (16.0)	2 (8.3)	4 (16.0)
Edema, peripheral	2 (8.0)	2 (8.3)	4 (16.0)
Skin disorders	8 (32.0)	6 (25.0)	8 (32.0)
Pruritus	1 (4.0)	3 (12.5)	2 (8.0)
Rash	1 (4.0)	3 (12.5)	2 (8.0)
Investigations	5 (20.0)	6 (25.0)	10 (40.0)
Increased creatine phosphokinase	3 (12.0)	2 (8.3)	1 (4.0)
Vascular disorders	8 (32.0)	6 (25.0)	5 (20.0)
Deep vein thrombosis	4 (16.0)	1 (4.2)	1 (4.0)
Hypotension	1 (4.0)	2 (8.3)	3 (12.0)
Respiratory disorders	6 (24.0)	3 (12.5)	6 (24.0)
Dyspnea	1 (4.0)	0	3 (12.0)
Nervous system disorders	9 (36.0)	1 (4.2)	3 (12.0)
Headache	3 (12.0)	0	2 (8.0)

required for the other. Daptomycin was similarly effective in PJI of either the hip or the knee, and the clinical success rates for both locations were higher than those observed in the comparator group (Table 4). At follow-up, clinical success in the mITT population was achieved for 12 of 24 (50.0%) and 11 of 23 (47.8%) patients in the daptomycin 6- and 8-mg/kg groups, respectively, and 8 of 21 (38.1%) patients in the comparator group. A sensitivity analysis, to evaluate the relative contributions of individual reasons for failure, demonstrated similar success rates in the 3 groups when each reason for failure was considered, including lack of clinical efficacy (Table 5).

Microbiological efficacy. Overall microbiological success at TOC (Table 4) was found for 12 of 24 (50.0%) and 12 of 23 (52.2%) patients in the daptomycin 6- and 8-mg/kg groups, respectively, and 8 of 21 (38.1%) patients in the comparator group. Microbiological success rates reflected clinical response.

Nine of 68 (13.2%) patients in the mITT population developed superinfections, including 3 of 24 patients (12.5%) in the daptomycin 6-mg/kg group and 6 of 21 patients (28.6%) in the comparator group. In 6 of these patients (2 in the daptomycin 6-mg/kg group and 4 in the comparator group), the baseline pathogens were eradicated and the superinfection led to a classification as microbiological failure.

TABLE 4 Clinical response and microbiological success in the mITT population at TOC visit

Outcome	No. with response/no. treated with daptomycin (%)		No. with response/no. treated with comparator (%)
	6 mg/kg	8 mg/kg	
Clinical response (overall)			
Success	14/24 (58.3)	14/23 (60.9)	8/21 (38.1)
Failure	9/24 (37.5)	7/23 (30.4)	11/21 (52.4)
Nonevaluable	1/24 (4.2)	2/23 (8.7)	2/21 (9.5)
Clinical response (in hip)			
Success	6/10 (60.0)	6/10 (60.0)	4/10 (40.0)
Failure	3/10 (30.0)	3/10 (30.0)	6/10 (60.0)
Nonevaluable	1/10 (10.0)	1/10 (10.0)	0/10 (0)
Clinical response (in knee)			
Success	8/14 (57.1)	8/13 (61.5)	4/11 (36.4)
Failure	6/14 (42.9)	4/13 (30.8)	5/11 (45.5)
Nonevaluable	0/14 (0)	1/13 (7.7)	2/11 (18.2)
Microbiological success			
Overall	12/24 (50.0)	12/23 (52.2)	8/21 (38.1)
<i>S. aureus</i>	7/14 (50.0)	7/14 (50.0)	4/10 (40.0)
MRSA	1/3 (33.3)	3/7 (42.9)	1/3 (33.3)
MSSA	6/11 (54.5)	4/7 (57.1)	3/7 (42.9)
CoNS	4/8 (50.0)	5/9 (55.6)	3/7 (42.9)

The MIC for daptomycin remained below the susceptibility breakpoint of ≤ 1 $\mu\text{g/ml}$ for all staphylococcal isolates in patients with microbiological failure, with no increases in daptomycin MIC for isolates obtained at the first surgery compared with isolates obtained at reimplantation.

DISCUSSION

Osteomyelitis is a complicated infectious process with various presentations and both acute and chronic types (17). As a measure of the difficulty of studying this disease, no antibiotic has been approved for bone and joint infection in the past 25 years. The current study in patients with PJI undergoing 2-stage revision arthroplasty allowed an opportunity to document microbiological eradication at EOT and follow-up in a homogeneous population. This is the first randomized, controlled trial studying 2 doses of daptomycin (6 and 8 mg/kg) compared with standard of care for PJI. The findings demonstrate that daptomycin administered for prolonged time periods was as well tolerated as standard treatment regimens. Enrollment was a challenge in this study. The rigorous entry criteria, which included microbiological confirmation at the baseline surgery, and the patients' willingness to consent to a 6-week treatment period resulted in a total of 74 patients being eligible for inclusion in the trial.

Prior antibiotics were permitted in this study. Since baseline cultures positive for *S. aureus*, taken at surgery number 1, were mandated for randomization into the study, the use of antibiotics prior to surgery number 1 did not confound the clinical outcome. It is also important to note that due to ethical concerns, routine standard-of-care antibiotics, except for daptomycin, were permitted by the protocol to be administered between surgery number 1 (removal of infected device) and confirmed positive surgical cul-

TABLE 5 Success rates based on reasons for failure as determined by investigator (mITT population)

Reason for failure	No. (%) of subjects treated with ^a :		
	Daptomycin, 6 mg/kg (n = 24)	Daptomycin, 8 mg/kg (n = 23)	Comparator (n = 21)
Nonevaluable	1	2	2
Success rate when reason for failure limited to nonevaluable	23 (95.8)	21 (91.3)	19 (90.5)
Discontinued study: clinical response	2	0	0
unsatisfactory			
Success rates when reason for failure limited to nonevaluable or lack of clinical efficacy	21 (87.5)	21 (91.3)	19 (90.5)
Discontinued study/study drug: adverse event	2	5	5
Success rates when reason for failure limited to nonevaluable, lack of clinical efficacy, or adverse event	19 (79.2)	16 (69.6)	14 (66.7)
Discontinued study: microbiological failure	0	1	0
Culture positive at surgery no. 2	5	1	6
Success rate when reason for failure limited to nonevaluable, lack of clinical efficacy, adverse event, or microbiological failure	14 (58.3)	14 (60.9)	8 (38.1)

^a Percentages are provided for success rates only.

tures, within 3 to 5 days. Given the treatment modality in osteomyelitis, with an average treatment duration of 6 weeks, it was determined that the use of prior antibiotics for 3 to 5 days after surgery number 1 and before starting study treatment would not confound clinical outcome. As the majority of the patients across all groups (>80% across all treatment groups) received antibiotics during this period, no sensitivity analysis to assess the impact of prior antibiotics was conducted.

In all treatment groups, antibiotic beads were used in 60/68 (88%) patients. The success rate for patients without antibiotic beads was 2/8 (25%) and in those with antibiotic beads it was 34/60 (57%) (not statistically significant). When comparing the success rates between treatment arms with and without antibiotic beads, the number of patients without beads was observed to be even smaller (3/24, 2/23, 3/21), and therefore, the effect of the antibiotic beads on the success rate could not be statistically evaluated. No sensitivity analysis was done to evaluate impact of different antibiotic beads.

Although the increases in CPK observed with both the 6- and 8-mg/kg doses of daptomycin in this study were numerically higher than those seen with the comparator group, they are consistent with other clinical trials of daptomycin at ≥ 6 mg/kg, where 2.5% to 8.3% of patients experienced CPK elevations (6, 9, 11, 14).

Most CPK elevations in our study were of short duration and did not result in musculoskeletal symptoms. In the 2 patients who were diagnosed as having rhabdomyolysis, daptomycin treatment was discontinued as suggested in the current prescribing information, and CPK levels in these patients returned to normal within 4 to 7 days of stopping daptomycin treatment. The AE profile in patients receiving daptomycin was similar to that in the comparator group, indicative that daptomycin at doses of 6 and 8 mg/kg was well tolerated over a prolonged period of treatment duration.

Treatment success did not differ between the 2 daptomycin groups, with both having a numerically higher success rate than the comparator group. However, the study was not designed to have statistical power to compare the groups. Although clinical success rates in this study were lower than that expected in clinical practice and as seen in other trials conducted with PJI patients undergoing 2-stage procedures, an additional sensitivity analysis based on reasons for clinical failure showed that success rates ranged from 88% to 91% (Table 5) when the reason for failure was limited to lack of clinical efficacy, excluding TEAEs and microbiological outcomes. Success rates in 2-stage exchange surgeries have been known to vary between 82% and 100% (12, 13, 19, 22). The difference is due to the definitions of outcomes used in this study, which were based on stringent criteria preferred by regulatory agencies rather than those used in clinical decision making (1, 3). For example, discontinuations due to AEs were considered failures in this study, whereas in clinical practice, a switch to alternative therapy that ended in a successful outcome would be considered a success (3). Similarly, the presence of the baseline pathogen at reimplantation in the absence of signs and symptoms of an active infection would not require additional antibiotic therapy or surgical intervention in clinical practice but would be considered a failure using the methodology of this study.

Previous published reports of daptomycin in bone and joint infections, including those with prosthetic joint infections, show success rates of 50% to 82% (15). An analysis of 67 patients with osteomyelitis from a registry of daptomycin use showed an overall success rate of 82% at follow-up, with a success rate of 88% in those who received >4 mg/kg. The subgroup of 17 patients with orthopedic devices also had an overall success rate of 82% (15). Antony et al. also found lower success rates (3/8, 37%) with the use of daptomycin at 4 mg/kg for PJI, whereas 17 of 22 (77%) patients receiving 6 mg/kg had successful outcomes (2), although this was not statistically significant.

In summary, daptomycin at 6 and 8 mg/kg in 49 patients was considered safe and appeared to be effective in managing staphylococcal PJI using a 2-stage revision arthroplasty technique, reflecting efficacy results from previous studies (2, 10, 15, 18). There was a trend for improved efficacy with daptomycin in the 49 treated patients compared with those observed with standard of care, indicating that daptomycin may represent an additional and convenient treatment alternative for management of the challenges associated with PJI. Further studies, however, are warranted to confirm these findings.

ACKNOWLEDGMENTS

This study has been registered with ClinicalTrials.gov (study no. NCT00428844).

We thank Douglas Osmon, Mayo Clinic, Rochester, MN, for the initial conception and study design. We especially express gratitude to Alistair Wheeler, Sunovion Pharmaceuticals, Inc., Marlborough, MA, for con-

ducting the clinical trial as well as for his input on drafting and reviewing the manuscript. Alistair Wheeler was employed at Cubist Pharmaceuticals, Inc., Lexington, MA, while the manuscript was being drafted and reviewed.

This work was supported by Cubist Pharmaceuticals, Inc.

I.B. was a paid consultant of Cubist Pharmaceuticals, Inc.; S.R., E.C., and S.Y. are employees of and stockholders in Cubist Pharmaceuticals, Inc.; G.K., D.A., and R.E. are paid consultants of Cubist Pharmaceuticals, Inc. In addition, R.E. is involved as faculty for educational programs for DePuy and also Smith & Nephew.

In addition to the authors, the following investigators and clinical contract research organizations participated in the phase 2 prosthetic joint infection study: L. Balter, Washington, DC; H. Bonilla, Akron, OH; M. Cancio, Tampa, FL; M. Gareca, Allentown, PA; N. Komilov, St. Petersburg, Russia; S. Linnik, St. Petersburg, Russia; R. Nathan, Idaho Falls, ID; D. Olysay, Springfield, IL; J. Parsonnet, Lebanon, NH; J. Parvizi, Philadelphia, PA; J. Peacock, Winston-Salem, NC; V. Prokhorenko, Novosibirsk, Russia; A. Seaton, Glasgow, United Kingdom; S. Schmitt, Cleveland, OH; J. Segretti, Chicago, IL; H. Simpson, Edinburgh, United Kingdom; R. Stienecker, Lima, OH; E. Volokitina, Kurgan, Russia; Pharmaceutical Product Development, LLC; ClinStar, LLC; and Pharm-Olam International, Ltd.

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