MAJOR ARTICLE

The Safety and Efficacy of Daptomycin for the Treatment of Complicated Skin and Skin-Structure Infections

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Daptomycin is the first available agent from a new class of antibiotics, the cyclic lipopeptides, that has activity against a broad range of gram-positive pathogens, including organisms that are resistant to methicillin, vancomycin, and other currently available agents. Daptomycin (4 mg/kg intravenously [iv] every 24 h for 7–14 days) was compared with conventional antibiotics (penicillinase-resistant penicillins [4–12 g iv per day] or vancomycin [1 g iv every 12 h]) in 2 randomized, international trials involving 1092 patients with complicated skin and skin-structure infections. Among 902 clinically evaluable patients, clinical success rates were 83.4% and 84.2% for the daptomycin- and comparator-treated groups, respectively (95% confidence interval, −4.0 to 5.6). Among patients successfully treated with iv daptomycin, 63% required only 4–7 days of therapy, compared with 33% of comparator-treated patients ($P < .0001$). The frequency and distribution of adverse events were similar among both treatment groups. Overall, the safety and efficacy of daptomycin were comparable with conventional therapy.

Complicated skin and skin-structure infections (cSSSIs), such as wound infections, major abscesses, or infected ulcers, typically involve gram-positive pathogens [1–3]. With the appearance of methicillin-resistant *Staphylococcus aureus* (MRSA) in the community, the emergence of vancomycin-intermediate and -resistant *S. aureus,* and the spread of vancomycin-resistant enterococci, it is increasingly difficult to find simple, safe, and effective treatment regimens for such infections [4, 5].

Daptomycin is a recently approved agent from a new class of antibiotics, the cyclic lipopeptides, that exhibits rapid, concentration-dependent bactericidal activity in vitro against a broad spectrum of gram-positive pathogens [6–12]. Daptomycin has a distinct mechanism of action [13–16] and is fully active against organisms that are resistant to currently available agents, including oxacillin, vancomycin, and linezolid. Furthermore, daptomycin has a very low frequency of spontaneous development of resistance in vitro; no transferable resistance elements have been identified to date [17].

On the basis of the findings of phase 1 and phase 2 clinical studies [8, 18, 19], 2 multicenter, randomized, controlled, evaluator-blinded trials were conducted to compare the safety and efficacy of daptomycin with that of conventional therapy (penicillinase-resistant penicillin [PRP] and vancomycin) for the treatment of patients with cSSSI requiring hospitalization.

PATIENTS, MATERIALS, AND METHODS

Patient eligibility. Study DAP-SST-98-01 was conducted from March 1999 through August 2001 at 64 institutions in the United States and at 5 institutions in South Africa. Study DAP-SST-99-01 was conducted from March 2000 through December 2000 at 42 sites in Europe, 20 sites in South Africa, 5 sites in Australia, and 3 sites in Israel. The study design was the same in

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both trials, with minor differences related to local regulatory requirements. The trials complied with guidelines for studies involving human subjects; all patients provided written informed consent.

Eligible patients were aged 18–85 years (in South Africa, they were aged ≤65 years). Primary inclusion criterion was a cSSSI that was due, at least in part, to gram-positive organisms and that required hospitalization and parenteral antimicrobial therapy for ≥96 h. Appropriate diagnoses included wound infections (e.g., surgical wounds, traumatic wounds, and bites), major abscesses, infected diabetic ulcers of the lower extremity, and infected ulcers due to other causes (e.g., uclers associated with vascular insufficiency or decubiti).

Patients were excluded from the studies if they had minor or superficial infections (e.g., simple abscesses, impetigo, and uncomplicated cellulitis), perirectal abscesses, gangrene, multiple infected ulcers at distant sites, or infections of third-degree burns. Patients were also excluded if they were known to have bacteremia at the time of enrollment, required curative surgery (e.g., amputation), or had concomitant infection at another site (e.g., endocarditis, osteomyelitis, or septic arthritis).

Study design and treatment. After performing the baseline evaluation, the investigator at each site assigned the comparator regimen—that is, PRP (cloxacillin, nafcillin, oxacillin, or flucloxacillin), 4–12 g iv q.d. in equally divided doses, or vancomycin, 1 g iv q12h by 60-min infusion—to be administered if the patient was randomized to comparator treatment (figure 1). Patients were then randomized (ratio, 1:1) to receive treatment for 7–14 days with either daptomycin (4 mg/kg iv q.d. by 30-min infusion) or a comparator regimen. Although patients were expected to receive only intravenous therapy, a change to oral medication was permitted if all of the following criteria were met: there was a compelling reason as specified in the protocol (e.g., unable to receive further intravenous therapy or a need to leave the hospital); the patient had received ≥4 days of intravenous therapy; there had been clear clinical improvement, as assessed by the blinded investigator; and the infecting organism was susceptible to an available oral therapy.

Clinical and microbiologic assessments. Outcomes were based primarily on clinical and microbiologic assessments performed at baseline (within 48 h before receipt of the first dose of study drug) and test-of-cure (6–20 days after receipt of the last dose). A blinded investigator assessed the site of infection for edema, erythema, fluctuance, induration, necrotic tissue, purulent drainage, tenderness, and ulceration. Cultures of samples from the infected area and of blood were processed at the local laboratory; gram-positive isolates were submitted to a central laboratory where MICs of all study antibiotics were determined using the broth microdilution method [20, 21].

Clinical response. At the test-of-cure evaluation, patients were considered by the blinded investigator to have had "clinical successes" if they had resolution of signs and symptoms such that no further antibiotic therapy was required. These patients were evaluated for clinical relapse or new infection at a poststudy visit 20–28 days after completion of therapy. Subjects were considered to have had "failure" if, at any point during the study, they had an inadequate response to therapy.

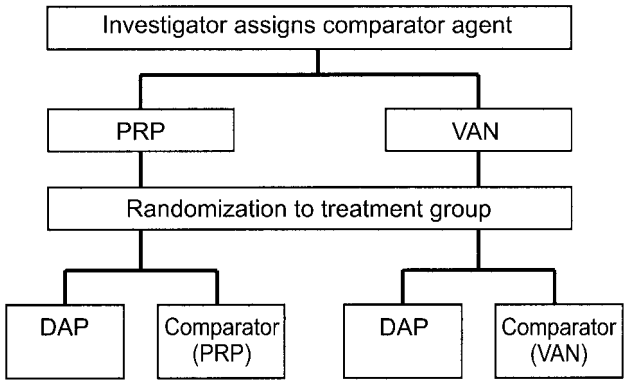

Figure 1. Study design for trials of complicated skin and skin-structure infections and daptomycin (DAP) therapy. Before randomization, the investigator assigned comparator agent (penicillinase-resistant penicillin [PRP] or vancomycin) that the patient should receive if randomized to comparator treatment group. Randomization was not stratified by this assignment. See Patients, Materials, and Methods for details. VAN, vancomycin.

Safety evaluation. The safety population comprised all patients who received ≥1 dose of study medication. Adverse events (AEs) and concomitant medications were monitored daily. The intensity of AEs was graded as mild, moderate, or marked ("severe") on the basis of the World Health Organization Toxicity Grading Scale. A serious AE (SAE) was defined as any AE that (1) was fatal, (2) was acutely life-threatening, (3) required or prolonged hospitalization, (4) caused persistent or significant disability, (5) was a congenital anomaly or birth defect, or (6) was an otherwise important medical event, such as allergic bronchospasm. Vital signs and clinical laboratory parameters, including clinical chemistry, hematology, and urinalysis findings, were assessed at each scheduled evaluation. Serum creatine phosphokinase (CPK) levels were determined at baseline, day 3, day 7, and every other day thereafter while the subject was receiving study medication [22].

Statistical analysis. The patient populations used for the efficacy analyses were intent-to-treat (ITT; i.e., all randomized patients with a cSSSI who received ≥1 dose of study medication), modified ITT (MITT; i.e., all patients in the ITT population with an infecting gram-positive organism isolated at baseline), clinically evaluable (i.e., all patients in the ITT population who met protocol-specified inclusion or exclusion criteria relating to the required assessments and to the absence of confounding factors, such as antibiotic administration for an intercurrent infection), and microbiologically evaluable (i.e., all patients in the clinically

Table 1. Demographic and baseline clinical characteristics of the intent-to-treat population.

Characteristic	Daptomycin group (n = 534)	Comparator group[a] (n = 558)
Sex		
Male	293 (55)	308 (55)
Female	241 (45)	250 (45)
Age		
Mean years (range)	51.5 (18–91)	51.9 (17–94)
⩾65 years	145 (27)	139 (25)
Race		
White	313 (59)	313 (56)
Black	145 (27)	151 (27)
Other	76 (14)	94 (17)
Comorbid conditions		
Diabetes mellitus	160 (30)	194 (35)
Peripheral vascular disease	103 (19)	128 (23)
Immunocompromise	18 (3)	19 (3)
Baseline diagnosis[b]		
Wound infection	224 (42)	254 (46)
Major abscess	138 (26)	124 (22)
Infected diabetic ulcer	61 (11)	72 (13)
Infected ulcer, not diabetic	70 (13)	75 (13)
Other infection	41 (8)	33 (6)
Bacteremia[c]	14 (3)	12 (2)
SIRS[d]	190 (36)	213 (38)

NOTE. Data are no. (%) of patients, unless otherwise indicated. SIRS, systemic inflammatory response syndrome.

[a] Cloxacillin, flucloxacillin, nafcillin, oxacillin, or vancomycin.

[b] On the basis of the investigators' description.

[c] Patients reported after enrollment to have bacteremia were allowed to continue in the study at the discretion of the investigator.

[d] Presence of ⩾2 of the following findings: temperature, >38°C or <36°C; heart rate, >90 beats/min; respiration rate, >20 breaths/min; or WBC count, $\geqslant 12 \times 10^3$ cells/μL or $<4 \times 10^3$ cells/μL or >10% bands.

evaluable population who had an infecting gram-positive organism isolated at baseline) populations.

The clinical success rate in a population was defined as the proportion of patients designated as having had clinical success; for the ITT and MITT populations, nonevaluable subjects were included in the denominator (i.e., they were effectively designated as being default failures). The 95% CI for the difference in success rates (the success rate for the comparator minus that for daptomycin) was calculated on the basis of the normal approximation to the binomial distribution. The statistical goal of these studies was to demonstrate the noninferiority of daptomycin in comparison with the comparator agents, which was defined as an upper bound of the 95% CI of <10% on the basis of the published recommendations of the Division of Anti-infective Drug Products of the US Food and Drug Administration [23]. With the sample sizes enrolled, each study was estimated to have a power of 80% to detect noninferiority.

Categorical variables were analyzed using Fisher's exact test, and continuous measures were analyzed using descriptive statistics or Student's t test, as appropriate. P values of ⩽.05 were considered to be significant.

RESULTS

Patients. Across both studies, 1092 patients were enrolled and received ⩾1 dose of study medication; these patients constituted the ITT efficacy population and safety population. The demographic and clinical characteristics of the treatment groups were well balanced at baseline (table 1). The distribution of subjects across the efficacy populations was similar for both treatment groups; ~83% of patients were clinically evaluable (table 2). More than 80% of the patients had an infecting organism identified, and the distribution of infecting organisms was similar in both groups (tables 3 and 4). Approximately 88% of the ITT population in each treatment group completed therapy; in both groups, the most common reason for premature discontinuation was treatment failure. These results indicate that the studies were well controlled and conducted.

Of 558 patients randomized to the comparator group, 337 (60%) were initially treated with a PRP, and 221 (40%) were initially treated with vancomycin. Concomitant aztreonam and/or metronidazole therapy was administered to 127 ITT patients (24%) treated with daptomycin and 148 patients (27%) treated with a comparator agent. Ancillary surgical procedures (typically, incision and drainage or wound debridement) were performed for 29% of subjects in each treatment group. More than 50% of patients in both groups received neither surgery nor concomitant antibiotics.

Outcomes. The 2 trials, individually and collectively, met the predefined statistical criteria for demonstrating that the efficacy of daptomycin therapy was not inferior to that of comparator therapy (table 5). For the combined ITT population, the success rates were 71.5% and 71.1% (95% CI, −5.8 to 5.0), and for the clinically evaluable population, the success rates were 83.4% and 84.2% (95% CI, −4.0 to 5.6) for daptomycin-

Table 2. Efficacy populations in a study of safety and efficacy of daptomycin for the treatment of complicated skin and skin-structure infections.

Population	No. (%) of patients: Daptomycin group (n = 534)	No. (%) of patients: Comparator group[a] (n = 558)
Intent-to-treat	534 (100)	558 (100)
Modified intent-to-treat	428 (80)	471 (84)
Clinically evaluable	446 (84)	456 (82)
Microbiologically evaluable	365 (68)	396 (71)

[a] Cloxacillin, flucloxacillin, nafcillin, oxacillin, or vancomycin.

Table 3. Infecting gram-positive organism at baseline for the modified intent-to-treat (MITT) population.

Organism	No. (%) of patients	
	Daptomycin group (n = 428)	Comparator group[a] (n = 471)
Staphylococcus aureus		
All	305 (71.3)	323 (68.6)
Methicillin-susceptible *S. aureus* [b]	231 (54.0)	239 (50.7)
Methicillin-resistant *S. aureus*[b]	40 (9.3)	47 (10.0)
Streptococcus pyogenes	92 (21.5)	103 (21.9)
Streptococcus agalactiae	30 (7.0)	41 (8.7)
Streptococcus dysgalactiae equisimilis	12 (2.8)	15 (3.2)
Viridans streptococci group	26 (6.1)	38 (8.1)
Enterococcus faecalis	45 (10.5)	61 (13.0)

NOTE. Species that are represented by <10 patients per treatment group are not shown. Totals add to >100% because 227 subjects in the MITT population had >1 gram-positive organism isolated at baseline; see table 4.

[a] Cloxacillin, flucloxacillin, nafcillin, oxacillin, or vancomycin.

[b] Methicillin susceptibility was determined only for isolates received by the central microbiology laboratories (ICON Laboratories [Farmingdale, NY] and Covance Laboratories [Indianapolis, IN]).

and comparator agent–treated patients, respectively. The response rates between treatment groups were comparable across baseline diagnoses (table 6). Detailed review of all treatment failures indicated no clinically meaningful patterns.

Clinical outcomes were comparable for both treatment groups among evaluable subjects with infecting gram-positive organisms (table 7). Among patients infected with both *S. aureus* and a β-hemolytic streptococcus, clinical success rates were 76% for those treated with daptomycin and 70% for those receiving comparator antibiotics. Gram-positive isolates cultured from patients after

Table 4. Combinations of multiple infecting gram-positive organisms at baseline in the modified intent-to-treat population.

Organism	No. (%) of patients	
	Daptomycin group (n = 428)	Comparator group[a] (n = 471)
Staphylococcus aureus and		
Streptococcus pyogenes	48 (11.2)	50 (10.6)[b]
Streptococcus agalactiae	14 (3.3)	25 (5.3)[c]
Streptococcus dysgalactiae equisimilis	5 (1.2)[b]	8 (1.7)
Viridans streptococci group	5 (1.2)[d]	1 (0.2)
Enterococcus faecalis	11 (2.6)	20 (4.2)
S. pyogenes and *E. faecalis*	1 (0.2)	0 (0)
S. agalactiae and		
S. dysgalactiae equisimilis	0 (0)	1 (0.2)
E. faecalis	3 (0.7)	1 (0.2)
S. dysgalactiae equisimilis and		
Viridans streptococci group	1 (0.2)	0 (0)
E. faecalis	1 (0.2)	0 (0)
Viridans streptococci group and		
Second Viridans streptococci group species	2 (0.5)	4 (0.8)
E. faecalis	1 (0.2)	7 (1.5)

NOTE. Categories are mutually exclusive and hierarchical. Species that are represented by <10 patients per treatment group are not shown.

[a] Cloxacillin, flucloxacillin, nafcillin, oxacillin, or vancomycin

[b] Includes 2 patients who also had *E. faecalis* isolated.

[c] Includes 2 patients who also had *E. faecalis* isolated and 1 patient who also had a viridans streptococci group species isolated.

[d] Includes 1 patient who also had a second viridans streptococci group species isolated.

Table 5. Clinical success rates, by study population.

Population	Daptomycin group		Comparator group[a]		95% CI[b]
	No. of patients	Success rate, %	No. of patients	Success rate, %	
Intent-to-treat	534	71.5	558	71.1	−5.8 to 5.0
Modified intent-to-treat	428	74.5	471	74.7	−5.5 to 5.9
Clinically evaluable	446	83.4	456	84.2	−4.0 to 5.6
Microbiologically evaluable	365	84.7	396	85.9	−3.8 to 6.3

[a] Cloxacillin, flucloxacillin, nafcillin, oxacillin, or vancomycin.
[b] The 95% CI around the difference in success rate (the rate in the comparator group minus that for the daptomycin group).

exposure to daptomycin showed the same distribution of MIC values as baseline (pretreatment) isolates.

Among the cohorts of patients assigned to each class of comparator agent (PRP and vancomycin) by the investigator before randomization (figure 1), clinical success rates for daptomycin and the comparator agent were similar (table 8). For both the daptomycin and the comparator treatment groups, success rates were higher among patients assigned to receive PRP than for those assigned to receive vancomycin.

Overall, 10.2% of the ITT population had their treatment regimen changed to oral therapy, primarily because of the need to leave the hospital. Among patients who were successfully treated with intravenous therapy alone, the duration of therapy was shorter for patients in the daptomycin group, with 63% requiring only 4–7 days of therapy, compared with 33% in the comparator group ($P < .0001$).

Among patients who were considered to have had clinical success at the test-of-cure visit, clinical relapse or recurrence was observed at the poststudy visit in 15 (4.2%) of 355 patients seen from the daptomycin treatment group and 20 (5.5%) of 367 patients seen from the comparator treatment group (95% CI, −4.4 to 1.9).

Safety and tolerability. The safety and tolerability of daptomycin, including the frequency and distribution of AEs, were similar to those for the comparator therapy (table 9). The majority of AEs were considered to be unrelated to study medication and were mild to moderate in intensity. In the safety population, 94 (18%) of 534 daptomycin-treated patients and 119 (21%) of 558 comparator agent–treated patients experienced ⩾1 AE considered to be related to study treatment. AEs of marked intensity (i.e., "severe" AEs) were reported for 60 patients (11%) in the daptomycin group and 49 patients (9%) in the comparator group. No single AE was reported to be severe in ⩾2% of patients in either treatment group.

The frequency and distribution of SAEs was similar in both groups, with ⩾1 SAE occurring in 10.9% of daptomycin-treated patients and 8.8% of comparator agent–treated patients. The only SAE to have occurred in ⩾1% of patients was cellulitis, which was reported in 7 patients (1.3%) in the daptomycin group and 0 patients in the comparator group. Eight patients in each treatment group died during the study; none of the deaths were considered to be treatment related.

Treatment discontinuations due to AEs occurred for only 15 patients (2.8%) in the daptomycin group and 17 patients (2.8%) in the comparator group; of these, the discontinuations for 7 and 11 patients, respectively, were considered possibly or probably treatment related. Infections and infestations represented the most frequent class of AEs leading to discontinuation and were reported for 5 patients in each treatment group.

Daptomycin has been reported to have the potential for muscle toxicity [22]; consequently, CPK levels were monitored closely. There were no differences between the treatment groups

Table 6. Clinical success rates, by investigator baseline diagnosis, for the clinically evaluable population.

Investigator diagnosis	Daptomycin group		Comparator group[a]		95% CI[b]
	No. of patients	Success rate, %	No. of patients	Success rate, %	
Wound infection	169	84	180	87	−4.8 to 10.1
Major abscess	102	92	92	88	−12.6 to 4.3
Infected ulcer, diabetic	47	66	56	70	−14.4 to 21.8
Infected ulcer, nondiabetic	47	79	58	83	−11.2 to 19.3

[a] Cloxacillin, flucloxacillin, nafcillin, oxacillin, or vancomycin.
[b] The 95% CI around the difference in success rate (the rate in the comparator group minus that for the daptomycin group).

Table 7. Clinical success rates, by infecting gram-positive organism, at baseline for the microbiologically evaluable population.

Treatment arm	Daptomycin group	Comparator group	95% CI
Staphylococcus aureus[b]			
Methicillin-susceptible	170/198 (85.9)	180/207 (87.0)	−5.6 to 7.8
Methicillin-resistant	21/28 (75.0)	25/36 (69.4)	−28.5 to 17.4
Streptococcus pyogenes	79/84 (94.0)	80/88 (90.9)	−11.1 to 4.9
Streptococcus agalactiae	23/27 (85.2)	22/29 (75.9)	−30.9 to 12.2
Streptococcus dysgalactiae	8/8 (100)	9/11 (81.8)	−48.6 to 12.2
Enterococcus faecalis	27/37 (73.0)	40/53 (75.5)	−16.3 to 21.3

NOTE. Data are *n*/*N* (%) of patients, unless otherwise indicated. For the purpose of this table, only pathogens for which daptomycin received a US Food and Drug Administration indication of clinical efficacy are considered.

[a] Cloxacillin, flucloxacillin, nafcillin, oxacillin, or vancomycin.

[b] Methicillin susceptibility was determined only for isolates received by the central microbiology laboratories (ICON Laboratories [Farmingdale, NY] and Covance Laboratories [Indianapolis, IN])

in the distribution of CPK values at baseline, during treatment, or after treatment. The frequency of treatment-emergent elevations in CPK level reported as AEs was also similar; the majority of these were associated with surgery (e.g., incision and drainage and debridement) or intramuscular injections.

Elevations in CPK levels were reported as treatment-emergent drug-related AEs for 11 patients (2.1%) in the daptomycin drug exposure group and 8 patients (1.4%) in the comparator group. Daptomycin therapy was discontinued by 2 patients as a result of elevated CPK levels. One patient, who had undergone a recent surgical procedure and had received multiple intramuscular injections, was noted to have elevated CPK levels without muscular symptoms on day 9 of therapy. The other patient experienced elevated CPK levels on day 10, with concurrent symptoms of mild-to-moderate weakness and upper-extremity muscle pain. Daptomycin therapy was discontinued for this patient, and all symptoms resolved over the following 72 h. CPK levels decreased rapidly and were within normal limits when evaluated at follow-up 2 weeks later. This episode represents the only AE observed in these studies that was consistent with daptomycin muscle toxicity.

Detailed review was also conducted of AEs consistent with hypersensitivity, as well as AEs affecting the hematopoietic, gastrointestinal (including liver), renal, neurologic (specifically, peripheral and cranial nerves), and cardiopulmonary systems. No statistically significant or clinically meaningful differences in frequency or distribution of these AEs were noted. Analysis of laboratory results and vital signs also indicated no clinically significant differences between drug exposure groups.

DISCUSSION

The increasing rate of antibiotic resistance among gram-positive pathogens has prompted interest in the development of new antimicrobial agents for these organisms. Daptomycin is a novel lipopeptide antibiotic with a distinct mode of action and rapid bactericidal activity in vitro. In these phase 3 studies, the safety and efficacy of daptomycin for the treatment of cSSSIs caused

Table 8. Clinical success rates, by class of comparator antibiotic, assigned by the investigator before randomization for the clinically evaluable population.

	Daptomycin group		Comparator group		
Class of comparator agent assigned before randomization[a]	No. of patients	Success rate, %	No. of patients	Success rate, %	95% CI[b]
Penicillinase-resistant penicillin	299	87.3	284[c]	90.5	−1.9 to 8.3
Vancomycin	111	81.1	172[d]	73.8	−17.4 to 2.9

[a] Class of comparator agent assigned was not available for 36 subjects in the daptomycin treatment group in Study 9801.

[b] The 95% CI around the difference in success rate (the rate for the comparator group minus that for the daptomycin group).

[c] Thirteen patients who were initially treated with penicillinase-resistant penicillin were subsequently switched to vancomycin therapy.

[d] Three patients who were initially treated with vancomycin were subsequently switched to penicillinase-resistant penicillin.

Table 9. Adverse events that occurred in ⩾2% of patients in either treatment group.

Adverse event	No. (%) of patients	
	Daptomycin group (n = 534)	Comparator group[a] (n = 558)
Constipation	33 (6.2)	38 (6.8)
Nausea	31 (5.8)	53 (9.5)
Injection site reaction	31 (5.8)	43 (7.7)
Headache	29 (5.4)	30 (5.4)
Diarrhea	28 (5.2)	24 (4.3)
Insomnia	24 (4.5)	30 (5.4)
Rash	23 (4.3)	21 (3.8)
Vomiting	17 (3.2)	21 (3.8)
Abnormal liver function test results	16 (3.0)	9 (1.6)
Pruritus	15 (2.8)	21 (3.8)
Elevated serum CPK level	15 (2.8)	10 (1.8)
Fungal infection	14 (2.6)	18 (3.2)
Hypotension	13 (2.4)	8 (1.4)
Urinary tract infection	13 (2.4)	3 (0.5)
Renal failure	12 (2.2)	15 (2.7)
Dizziness	12 (2.2)	11 (2.0)
Anemia	11 (2.1)	13 (2.3)
Dyspnea	11 (2.1)	9 (1.6)
Fever	10 (1.9)	14 (2.5)
Limb pain	8 (1.5)	11 (2.0)
Hypertension	6 (1.1)	11 (2.0)
Dyspepsia	5 (0.9)	14 (2.5)
Arthralgia	5 (0.9)	12 (2.2)

NOTE. CPK, creatine phosphokinase.

[a] Cloxacillin, flucloxacillin, nafcillin, oxacillin, or vancomycin.

by gram-positive organisms was compared with the safety and efficacy of current standard therapy (i.e., PRPs and vancomycin).

Daptomycin therapy was clinically and statistically comparable to standard therapy for the treatment of cSSSIs. The results were robust and consistent across all predefined patient populations, across different species of infecting gram-positive organisms, across different types of infection, and for primary clinical outcomes (test of cure) and posttreatment relapse rates. MIC_{90} values for daptomycin were uniformly low for the most prevalent isolates, including methicillin-susceptible *S. aureus* (MSSA), MRSA, and streptococcal species. For both treatment groups, success rates for MRSA were lower than for MSSA, most likely reflecting the comorbidities prevalent among these patients [24–27]. There was no trend toward increased MICs among isolates cultured from patients treated with daptomycin, including those who had treatment failure.

Daptomycin was also comparable to each class of comparator agent (PRPs and vancomycin) considered separately. This analysis was facilitated by the fact that, before randomization, the investigator indicated for each patient the comparator agent to be administered in the event that the patient was not randomized to receive daptomycin. Approximately 40% of the patients were assigned to receive vancomycin. In almost all instances, this reflected the investigator's judgment that the patient was at risk for infection with MRSA. Baseline cultures indicated that ~10% of patients had MRSA infection; nevertheless, the patients assigned to receive vancomycin had poorer outcomes than did the patients assigned to receive PRPs. This trend was apparent regardless of whether the patient was, on the basis of randomization, treated with daptomycin or with the previously assigned comparator agent. These results suggest that, even in the absence of MRSA infection and independent of treatment, the outcomes were influenced by the clinical risk factors (e.g., comorbid disease and recent hospitalization) that prompted the investigator's concern about drug-resistant pathogens.

The clinical success rates (83.4%–84.2% for the clinically evaluable population and 84.7%–85.9% for the microbiologically evaluable population) observed in this trial are comparable with those for other antimicrobial agents recently approved for the treatment of cSSSIs. In a trial that compared quinupristin-dalfopristin and conventional agents (cefazolin, oxacillin, or vancomycin), the clinical success rates in the clinically evaluable population were 68% (197 of 289 patients) and 71% (193 of 273 patients), respectively [28]. In a study comparing linezolid with oxacillin in the treatment of cSSSI, success rates in the clinically evaluable population were 89% and 86%, respectively [29]. That study included few patients with infected surgical or traumatic wounds (<15%) and excluded patients infected with MRSA.

Daptomycin was safe and well tolerated. The frequency, distribution, and severity of AEs were similar for daptomycin and standard therapy. Discontinuations due to AEs were uncommon, and there were no deaths assessed as related to study medication. Gastrointestinal disorders were the most commonly reported treatment-emergent AE in both groups. There were no clinically significant differences between daptomycin and standard therapy for any hematologic or clinical laboratory parameters.

In prior phase 1 studies, 2 subjects who received daptomycin (4 mg/kg iv q12h) for ~1 week experienced muscle pain, weakness, and elevated serum CPK levels, all of which resolved completely and rapidly after discontinuation of daptomycin therapy [30]. Subsequent animal studies indicated that the frequency and severity of muscle effects decreased appreciably with increasing dosage interval, suggesting that once-daily dosing of daptomycin might minimize the potential for these AEs [22]. This was supported by a study of healthy volunteers in which daptomycin was well tolerated when it was administered once daily at doses as high as 8 mg/kg for 14 days, with no drug-

related elevations in the CPK level observed [18]. In the large phase 3 trials reported here, CPK levels were closely monitored and revealed no clinically or statistically significant differences between once-daily daptomycin and standard therapy. Across all phase 2 and 3 studies, 1342 patients received once-daily daptomycin at 4 or 6 mg/kg; only 2 patients (0.2%) (including the patient in this study) experienced drug-related muscle AEs with symptoms of myalgia and/or muscle weakness and significantly elevated CPK levels. In both cases, clinical symptoms and laboratory findings resolved rapidly and completely after the discontinuation of daptomycin therapy.

Thus, these trials achieved their primary goal and demonstrated with statistical rigor that the safety and efficacy of daptomycin (4 mg/kg iv q.d.) is comparable to that of standard therapy for the treatment of cSSSI. Additional clinical considerations, including safety profile and rapidity of response, suggest that daptomycin may represent an attractive treatment alternative. Among 450 patients receiving quinupristin-dalfopristin in 2 cSSSI trials, treatment was discontinued because of venous AEs in 12%, compared with 2% of those who received comparator therapy [28]. Arthralgia and myalgia have been observed in up to 10% of patients treated with quinupristin-dalfopristin [31]. Linezolid use has been associated with anemia, leukopenia, pancytopenia, and thrombocytopenia. The latter has been reported to be related to treatment exceeding 14 days in duration [32], prompting suggestions that platelet counts should be closely monitored in patients treated for $\geqslant$10 days [33].

Several observations suggest that, in clinical use, there may be advantages to daptomycin. In a post hoc analysis of patients successfully treated with intravenous therapy alone, the duration of treatment was shorter for persons receiving daptomycin than for those receiving conventional therapy. Furthermore, although the daptomycin recipients received shorter courses of intravenous therapy, they tended to have a low incidence of relapsing or recurrent infection when evaluated 3–4 weeks after the end of treatment.

In summary, daptomycin is the first available agent from a new class of antibiotics, the cyclic lipopeptides. It is active in vitro against a wide range of gram-positive organisms, including those that are resistant to all other currently available drugs, such as vancomycin and linezolid. These 2 randomized, controlled clinical trials demonstrate that daptomycin given at 4 mg/kg once per day is as safe and effective as standard therapy for the treatment of cSSSI caused by gram-positive pathogens.

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