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 (cSSIs), 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 cSSI 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
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 ³96 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., ulcers 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 success.** 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.

**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 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
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, non-evaluable 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 non-inferiority 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 non-inferiority.

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 $\leq .05$ were considered to be significant.

RESULTS

Patients. Across both studies, 1092 patients were enrolled and received $\geq 1$ 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; $\sim 83\%$ 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-
and comparator agent-treated patients, respectively. The re-
sponse 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
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, 1.9 to 4.4).

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 5. Clinical success rates, by study population.

<table>
<thead>
<tr>
<th>Population</th>
<th>Daptomycin group</th>
<th>Comparator group∗</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. of patients</td>
<td>Success rate, %</td>
</tr>
<tr>
<td>Intent-to-treat</td>
<td>534</td>
<td>71.5</td>
</tr>
<tr>
<td>Modified intent-to-treat</td>
<td>428</td>
<td>74.5</td>
</tr>
<tr>
<td>Clinically evaluable</td>
<td>446</td>
<td>83.4</td>
</tr>
<tr>
<td>Microbiologically evaluable</td>
<td>365</td>
<td>84.7</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Investigator diagnosis</th>
<th>Daptomycin group</th>
<th>Comparator group∗</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. of patients</td>
<td>Success rate, %</td>
</tr>
<tr>
<td>Wound infection</td>
<td>169</td>
<td>84</td>
</tr>
<tr>
<td>Major abscess</td>
<td>102</td>
<td>92</td>
</tr>
<tr>
<td>Infected ulcer, diabetic</td>
<td>47</td>
<td>66</td>
</tr>
<tr>
<td>Infected ulcer, nondiabetic</td>
<td>47</td>
<td>79</td>
</tr>
</tbody>
</table>

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.

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

**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.

- Daptomycin group: 299 patients
- Comparator group: 284 patients
- 95% CI: -1.9 to 8.3

- Daptomycin group: 111 patients
- Comparator group: 172 patients
- 95% CI: -17.4 to 2.9

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

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

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

*Thirty patients who were initially treated with vancomycin were subsequently switched to penicillinase-resistant penicillin.*
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. MIC90 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 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