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Randomized Comparison of Linezolid (PNU-100766) versus Oxacillin-Dicloxacillin for Treatment of Complicated Skin and Soft Tissue Infections

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This randomized, double-blind, multicenter trial compared the efficacy and safety of linezolid, an oxazolidinone, with those of oxacillin-dicloxacillin in patients with complicated skin and soft tissue infections. A total of 826 hospitalized adult patients were randomized to receive linezolid (600 mg intravenously [i.v.]) every 12 h or oxacillin (2 g i.v.) every 6 h; following sufficient clinical improvement, patients were switched to the respective oral agents (linezolid [600 mg orally] every 12 h or dicloxacillin [500 mg orally] every 6 hours). Primary efficacy variables were clinical cure rates in both the intent-to-treat (ITT) population and clinically evaluable (CE) patients and microbiological success rate in microbiologically evaluable (ME) patients. Safety and tolerability were evaluated in the ITT population. Demographics and baseline characteristics were similar across treatment groups in the 819 ITT patients. In the ITT population, the clinical cure rates were 69.8 and 64.9% in the linezolid and oxacillin-dicloxacillin groups, respectively ($P = 0.141$; 95% confidence interval −1.58 to 11.25). In 298 CE linezolid-treated patients, the clinical cure rate was 88.6%, compared with a cure rate of 85.8% in 302 CE patients who received oxacillin-dicloxacillin. In 143 ME linezolid-treated patients, the microbiological success rate was 88.1%, compared with a success rate of 86.1% in 151 ME patients who received oxacillin-dicloxacillin. Both agents were well tolerated; most adverse events were of mild-to-moderate intensity. No serious drug-related adverse events were reported in the linezolid group. These data support the use of linezolid for the treatment of adults with complicated skin and soft tissue infections.

Skin and soft tissue infections are frequently encountered in clinical practice, and gram-positive bacteria are a leading cause (18). These infections are classified as complicated when surgical intervention is required and/or the infectious process is suspected or confirmed to involve deeper tissue (e.g., subcutaneous tissues, fascia, and/or skeletal muscle) (18). Complications of improperly treated skin and soft tissue infections may include endocarditis, osteomyelitis, brain abscess or meningitis, lung abscess, or pneumonia. Skin and soft tissue infections include superficial infections such as erysipelas, cellulitis, simple abscesses, furuncles, wound infections, and deeper infections such as necrotizing fasciitis, myositis, and gas gangrene. *Streptococcus pyogenes*, *Staphylococcus aureus*, *Streptococcus agalactiae*, and group C and G streptococci are the most commonly involved pathogens (27, 28). Intravenous antibiotics are often used in patients with complicated infections, and most patients are hospitalized for management of their infection. In addition, some patients acquire such infections while hospitalized for surgical procedures or trauma (18).

The usual treatment for most gram-positive skin and soft tissue infections is a penicillinase-resistant penicillin or a cephalosporin (15). However, the worldwide emergence of pathogens with decreased susceptibility to available therapies has created a need for new antimicrobial agents (3, 4, 11, 12, 20, 21, 29, 30). Linezolid (PNU-100766) is the first of the oxazolidinones, a new class of antimicrobial agents that inhibit bacterial protein synthesis by blocking formation of the initiation complex (26, 31). Linezolid has demonstrated in vitro and in vivo antibacterial activity against staphylococci, streptococci, and enterococci, including resistant strains such as methicillin-resistant *S. aureus* (MRSA), penicillin-resistant *Streptococcus pneumoniae*, and vancomycin-resistant enterococci (6, 8, 9, 10, 14, 17, 19, 23, 31).

In early, phase II clinical trials, linezolid was safe and effective in the treatment of gram-positive skin and soft tissue infections and pneumonia (S.-K. Cammarata, B. Hafkin, W. M. Todd, and D. H. Batts, Am. J. Respir. Crit. Care Med. **159**(Suppl.)**:** 844, part 2, abstr., 1999; S.-K. Cammarata, B. Hafkin, D. M. Demke, S. M. Eckert, and D. H. Batts, Clin. Microbiol. Infect. **5**(Suppl. 3)**:**133, abstr., 1999). This randomized trial compared the efficacy and safety of linezolid with oxacillin-dicloxacillin in the treatment of adults with complicated skin and soft tissue infections.

MATERIALS AND METHODS

Study design. This prospective, randomized, double-blind, double-dummy, multicenter, multinational study was conducted from November 1998 to June 1999 at 133 sites. Study objectives included assessment of the comparative clinical and microbiological efficacy, safety, and tolerability of linezolid versus oxacillin-dicloxacillin in the treatment of adults with complicated skin and soft tissue infections. The study consisted of (i) a baseline or screening visit, (ii) an end-of-treatment visit, and (iii) a follow-up visit 15 to 21 days after the final dose of study medication. A test-of-cure (TOC) evaluation was conducted at the follow-up visit. Patients underwent daily clinical assessments while hospitalized (one intravenous [i.v.] dose minimum) and every 6 days after discharge. The protocol, informed consent, and all other forms of patient information related to the study were reviewed and approved by each investigator's institutional review

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board and/or independent ethics committee. All patients provided written informed consent prior to enrollment.

Patient selection. Hospitalized patients who were at least 18 years of age with a suspected gram-positive complicated skin and soft tissue infection were eligible for participation. Infections included those that involved deep soft tissue (e.g., major abscess, infected ulcer, major burn, or deep and extensive cellulitis) with at least two of the following symptoms: drainage and/or discharge, erythema, fluctuance, heat and/or localized warmth, pain and/or tenderness to palpation, or swelling and/or induration. At least one of the following conditions must have been present: fever (defined as body temperature of >38°C [orally]), elevated total peripheral white blood cell (WBC) count (>10,000/mm^3), or >15% immature neutrophils (bands) irrespective of total peripheral WBC count. In addition, patients must have been able to take i.v. and oral (p.o.) medications, have an accessible infection site for Gram staining and culture, and have been willing to return for end-of-treatment and follow-up visits.

Patients meeting any of the following criteria were excluded from the study: previous antibiotic therapy for >24 h within 7 days of study entry unless the pathogen showed drug resistance or the treatment failed (no clinical improvement after 3 days); uncomplicated skin infection; abscesses requiring only surgical drainage; self-limited infection; diabetic foot ulcer, decubitus ulcer, ischemic ulcers, necrotizing fasciitis, gas gangrene, or burns on more than 20% of total body surface; superinfected eczema; infections requiring concomitant systemic corticosteroids or antimicrobial agents (other than aztreonam); infections complicated by prosthetic materials; inability to comply with treatment period and evaluation; treatment with another investigational medication within the past 30 days; or prior enrollment in this or another linezolid protocol. Exclusionary medical conditions included pheochromocytoma, carcinoid syndrome, liver disease, osteomyelitis, uncontrolled hypertension, neutropenia, untreated hyperthyroidism, and hypersensitivity to study medications. In addition, female patients were excluded if they were pregnant, nursing, or unable to take adequate contraceptive precautions.

Treatment. Patients were randomized in a 1:1 ratio to receive either linezolid (supplied by Pharmacia & Upjohn, Kalamazoo, Mich.) (600 mg i.v.) every 12 h or oxacillin (Marsam Pharmaceuticals, Inc., Cherry Hill, N.J.) (2 g i.v.) every 6 h for 10 to 21 days. Linezolid and placebo were alternated every 6 h to maintain the study blind. Patients in both treatment groups who required empiric gram-negative coverage were allowed to receive i.v. aztreonam (1 to 2 g) three or four times daily as appropriate. When a patient demonstrated clinical improvement, the patient could be switched to oral study medication at the investigator's discretion. Patients initially randomized to i.v. linezolid were switched to linezolid tablets (600 mg p.o.) every 12 h (study medication and placebo were alternated every 6 h to maintain the study blind), while those initially randomized to oxacillin were switched to dicloxacillin (Apothecon, Princeton, N.J.) (500 mg capsules p.o.) every 6 h. In each treatment group, placebo dummies were identical to the active antibiotic for the respective group.

Clinical assessments. Clinical evaluations including a medical history and physical examination, with vital signs, clinical observations (i.e., chills, drainage and/or discharge, swelling and/or induration, tenderness and/or pain to palpation, heat and/or localized warmth, and fluctuance), clinical laboratory assays (i.e., hematology, clinical chemistries, urinalysis), and electrocardiogram, were performed at baseline, during inpatient and/or outpatient treatment, at the end of treatment, and at follow-up. These assessments also were performed as patients were switched from i.v. to p.o. therapy. The follow-up evaluation scheduled for 15 to 21 days following treatment was considered the TOC evaluation. TOC assessments were based upon improvement and/or resolution of clinical signs and symptoms of the skin and soft tissue infection.

Microbiological assessments. Prior to the first infusion of either study drug, deep culture specimens of the area contiguous to the primary infected area were obtained for Gram's stain, culture, and susceptibility testing. All isolated pathogens were submitted to a central laboratory for identification. Complete identification of each bacterial isolate was performed, and each organism was classified as a pathogen or a nonpathogen. Susceptibility testing was performed in accordance with National Committee for Clinical Laboratory Standards guidelines. Sponsor-defined breakpoints were used for linezolid susceptibility testing (≤4 μg/ml, sensitive; >4 μg/ml, resistant). Patients whose cultures grew gram-positive or gram-negative pathogens that were not susceptible to study medications were discontinued from the study unless they demonstrated clinical improvement and did not require concomitant antimicrobial therapy (other than aztreonam).

Efficacy variables. Primary efficacy variables were clinical outcome and microbiological outcome based on resolution or improvement of clinical signs and symptoms of infection at the end of treatment compared with those at baseline. Objective and subjective clinical observations recorded throughout the course of the study included anatomical site of infection, extent of infection, degree of involvement, infected-site description, and body temperature. Criteria for assessing clinical outcome were as follows: cure was defined as resolution of baseline clinical signs and symptoms of infection or improvement such that no further antimicrobial treatment was necessary after at least 5 days and 10 doses of study medication; failure was defined as a need for nonstudy antibiotic due to lack of efficacy after at least 2 days and 8 doses of study medication or absence of clinical assessments at the end of treatment and follow-up; indeterminate response was defined as clinically improved or cured at the end of treatment and no assessment at TOC; and missing was defined as those patients receiving less than 2 days of therapy or fewer than 8 doses. Criteria for assessing microbiological outcome were as follows: success was defined as documented eradication (absence of original pathogen[s] from culture at TOC) or presumed eradication (clinical cure at TOC with no microbiological data); failure was defined as documented persistence (presence of original pathogen [one or more] from culture at TOC) or presumed persistence, superinfection, or reinfection (clinical failures at TOC with no microbiological data or those who received nonstudy antibiotic therapy); indeterminate was defined as those patients classified as indeterminate in clinical assessment; and missing was defined as the absence of clinical determination and no microbiological data at TOC.

Other variables evaluated included body temperature, WBC counts, clinical signs and symptoms of infection (chills, erythema, drainage and/or discharge, swelling and/or induration, tenderness and/or pain to palpation, heat and/or localized warmth, and fluctuance), and selected organism or pathogen eradication rates.

Safety variables. The safety of linezolid and oxacillin-dicloxacillin therapy was monitored throughout the study by physical examination, vital signs, laboratory evaluations, and assessment of adverse events. All patients who received at least one dose of study medication were included in the safety analysis. Physical examination was conducted at baseline and follow-up visits, and vital signs were assessed at all visits. The following laboratory evaluations were conducted: hematology, chemistry, urinalysis, pregnancy test (for females of childbearing potential), site culture and Gram staining, blood culture, and bacterial isolate susceptibility testing. Adverse events were reported from the time of first dose of study drug to the final study visit and were monitored until they resolved or until the patient's participation in the study ended.

Population for analysis. Three patient populations were evaluated in this study: the intent-to-treat (ITT) population, the clinically evaluable patients, and the microbiologically evaluable patients. The ITT population included all patients who received at least one dose of double-blind study drug. Clinically evaluable patients included patients from the ITT population who (i) had not received concomitant antibiotic therapy (other than aztreonam) during the study, (ii) had received at least 7 days and 24 doses of study medication (unless the patient discontinued the study for any reason other than lack of efficacy), (iii) had taken at least 80% of prescribed study medications throughout the study and did not miss two or more consecutive doses through day 7 of treatment, and (iv) had a postbaseline assessment during the follow-up period (15 to 21 days posttreatment). Microbiologically evaluable patients included clinically evaluable patients who had a confirmed pathogen from the infection site or blood culture at baseline that was not resistant to study medications.

Statistical methods. Analyses were performed to compare the efficacy and safety of linezolid with oxacillin-dicloxacillin. All data listings, summaries, and statistical analyses were generated using the Statistical Analysis System (version 6; SAS Institute Inc., Cary, N.C.). All statistical tests were two-sided, and P values of ≤0.05 were considered statistically significant. Analyses of efficacy variables were performed for the ITT, clinically evaluable, and microbiologically evaluable patient populations. Assuming each treatment group would yield a 90% success rate, 142 evaluable patients per treatment group were required to determine, with 80% power, equivalence between the groups to within 10%. Assuming an evaluability rate of 45%, this translated to a requirement of 316 enrolled patients per treatment group. All 95% confidence intervals (95% CI) were based on the normal approximation to the binomial distribution and were considered consistent with equivalence if the following conditions were met: there were at least 142 patients per treatment group, the CI included 0, and the lower limit of the CI exceeded −10%. Due to the expected small numbers of evaluable patients in each center, terms for investigator effect and treatment group-by-investigator interaction were not included in the models for statistical analysis.

Comparability of baseline demographics between treatment groups was assessed using one-way analysis of variance fixed-effects models (age, weight, vital signs, and selected quantitative laboratory analyses) or using the chi-square test for two-way contingency tables (gender, race, physical examination, clinical signs and symptoms). Patient clinical outcome was assessed by clinical cure rate (the number of cures divided by the number of cures and failures) in the clinically evaluable patient cohort. Microbiological outcome was assessed by the microbiological success rate, defined as the number of successes divided by the sum of the number of successes and failures in the microbiologically evaluable patient cohort. Comparability of clinical cure rates and microbiological success rates were assessed using 95% CI for the difference in these rates and a chi-square test for homogeneity of proportions for the distribution of clinical cures, microbiological successes, and failures between treatment groups.

RESULTS

Patient demographics. Of the 826 patients enrolled in 133 centers, 403 and 423 were randomized to the linezolid and oxacillin-dicloxacillin treatment groups, respectively. The ITT population consisted of 819 patients who received at least one dose of study drug (400 received linezolid and 419 received oxacillin-dicloxacillin). The study evaluation groups and rea-

TABLE 1. Disposition of patients

Population[a] or detail	No. (%) treated with:	
	Linezolid	Oxacillin-dicloxacillin
ITT patients	400 (100)	419 (100)
Clinically evaluable patients	298 (74.5)	302 (72.1)
Reasons for nonevaluability:		
Prior antibiotic usage	3 (0.8)	4 (1.0)
Insufficient therapy	29 (7.3)	43 (10.3)
Concomitant antibiotics	11 (2.8)	15 (3.6)
Noncompliance with regimen	39 (9.8)	47 (11.2)
No clinical outcome postbaseline	64 (16.0)	64 (15.3)
Microbiologically evaluable patients	143 (35.8)	151 (36.0)
Reasons for nonevaluability:		
Clinically nonevaluable	102 (25.5)	117 (27.9)
No baseline pathogens	189 (47.3)	201 (48.0)
Baseline pathogen resistant to study medication	11 (2.8)	11 (2.6)

[a] Patients may have had multiple reasons for nonevaluability. All reasons are summarized; therefore, percentages may total more than 100%.

sons for nonevaluability are shown in Table 1. Six hundred patients (298 receiving linezolid and 302 receiving oxacillin-dicloxacillin) made up the clinically evaluable subgroup. The microbiologically evaluable patients included 143 linezolid and 151 oxacillin-dicloxacillin patients. The most common reason for clinical nonevaluability was lack of a baseline assessment. Lack of a baseline pathogen was the most frequent reason for microbiological nonevaluability. Demographics and baseline characteristics of the ITT population (Table 2) and clinically evaluable patients were similar in both treatment groups. The most common complicated skin and soft tissue diagnoses at baseline were cellulitis, skin abscess, and erysipelas. The majority of patients in the study had relatively serious infections, with 319 of 397 (80.4%) of the linezolid-treated patients and 322 of 417 (77.2%) of the oxacillin-dicloxacillin-treated patients having deep involvement of the skin at the primary site of infection. Clinically relevant pathogens isolated at baseline included: *S. aureus* in 140 linezolid patients and 143 oxacillin-dicloxacillin patients; *S. pyogenes* in 41 linezolid patients and 46 oxacillin-dicloxacillin patients; and *S. agalactiae* in 10 linezolid patients and 12 oxacillin-dicloxacillin patients.

Treatment. The total durations of treatment (i.v. and p.o.) were similar in both treatment groups; the mean duration of treatment was 13.4 ± 5.4 days in the linezolid group and 13.4 ± 6.0 days in the oxacillin-dicloxacillin group. (Unless otherwise noted, values are means ± standard deviations.) Among the clinically evaluable patients, the total durations of treatment (i.v. and p.o.) also were similar, with a mean duration of 14.3 ± 4.6 days in the linezolid group and 14.1 ± 4.6 days in the oxacillin-dicloxacillin group. Most ITT patients in both treatment groups received ≤5 days of i.v. therapy, with a mean duration of 4.7 ± 3.3 days for linezolid-treated patients and 4.7 ± 3.1 days for oxacillin-dicloxacillin-treated patients. Similar results were observed in clinically evaluable patients.

Among the ITT patients, 49 patients (12.3%) in the linezolid group and 77 patients (18.4%) in the oxacillin-dicloxacillin group received concomitant noninvestigational antimicrobial therapy after the first day of study medication. The most common classes of antimicrobials used were cephalosporins, penicillins, fluoroquinolones, and parenteral aminoglycosides. Of these patients, 26 linezolid-treated patients (6.5%) and 40 oxacillin-dicloxacillin-treated patients (9.5%) used cephalosporins, and eight linezolid-treated patients (2.0%) and 10 oxacillin-dicloxacillin-treated patients (2.4%) used topical antibiotics.

Discontinuations. Overall, the percentages of patients who completed treatment and follow-up were similar between treatment groups (336 of 403 [84%] in the linezolid group and 327 of 423 [78%] in the oxacillin-dicloxacillin group). In the ITT population, more patients in the oxacillin-dicloxacillin group (70 of 419 [16.7%]) than in the linezolid group (43 of 400 [10.8%]) discontinued participation during treatment. The most frequent reason for discontinuation, regardless of treatment group, was lack of efficacy (9 of 400 [2.3%] patients in the linezolid group and 15 of 419 [3.6%] patients in the oxacillin-dicloxacillin group). Similarly, the percentage of patient discontinuations during follow-up was slightly higher in the oxacillin-dicloxacillin group (73 of 419 [17.4%] patients) than in the linezolid group (54 of 400 [13.5%] patients), with loss to follow-up representing the most common reason for discontinuation (27 of 400 [6.8%] patients in the linezolid group and 32 of 419 [7.6%] patients in the oxacillin-dicloxacillin group).

Efficacy. In the ITT population, the clinical cure rates at the TOC visit were comparable in the two treatment groups, with 279 of 400 (69.8%) linezolid-treated patients and 272 of 419 (64.9%) oxacillin-dicloxocillin-treated patients achieving a clinical cure ($P = 0.141$; 95% CI, −1.58 to 11.25 [point estimate, 4.9]). In clinically evaluable patients, clinical cure rates at the TOC visit also were comparable in linezolid and oxacillin-dicloxacillin groups (264 of 298 [88.6%] patients versus 259 of 302 [85.8%] patients, respectively) ($P = 0.300$; 95% CI, −2.5 to 8.2 [point estimate, 2.8]) (Table 3). Subgroup analysis of clinical outcome by gender, age, and race demonstrated similar results between treatment groups, except for males in the ITT population, for whom cure rates were 85.3% (174 of 204 patients) and 76.7% (171 of 223 patients) in the linezolid and

TABLE 2. Demographic and baseline characteristics for ITT population

Characteristic	No. (%) of ITT patients treated with:	
	Linezolid ($n = 400$)	Oxacillin-dicloxacillin ($n = 419$)
Gender [no. (%)[a]]		
Male	252 (63.0)	255 (60.9)
Female	148 (37.0)	164 (39.1)
Mean age ± SD (yr)	46.8 ± 17.1	49.2 ± 18.5
Mean weight ± SD (kg)	79.1 ± 22.7	79.0 ± 23.0
Race [no. (%)]		
White	227 (56.8)	230 (54.9)
Black	49 (12.3)	69 (16.5)
Asian or Pacific Islander	38 (9.5)	42 (10.0)
Other or unknown	86 (21.5)	78 (18.6)
Diagnosis [no. (%)[a]]		
Cellulitis	178 (44.8)	186 (44.6)
Skin abscesses	58 (14.6)	64 (15.3)
Skin ulcer	15 (13.8)	14 (3.4)
Erysipelas	41 (10.3)	40 (9.6)
Infected surgical incision	25 (6.3)	26 (6.2)
Infected wound	24 (6.0)	40 (9.6)
Infected bite	7 (1.8)	3 (0.7)
Other	49 (12.3)	43 (10.3)
Missing	0	1 (0.2)
Mean duration of infection (days)	5.6 ± 7.8	6.2 ± 15.1

[a] Percentages are based on the number of patients reporting.

TABLE 3. Assessment of efficacy in ITT, clinically evaluable, and microbiologically evaluable patients

Patient group	Treatment	Total no. (%) of patients assessed[a]	No. (%) of patients with assessment		*P* (95% CI[b] [point estimate])[b]
			Cure	Failure[c]	
ITT	Linezolid	400 (100)	279 (69.8)	121 (30.8)	0.141 (−1.58, 11.25 [4.9])
	Oxacillin-dicloxacillin	419 (100)	272 (64.9)	147 (35.1)	
Clinically evaluable	Linezolid	298 (100)	264 (88.6)	34 (11.4)	0.300 (−2.5, 8.2 [2.8])
	Oxacillin-dicloxacillin	302 (100)	259 (85.8)	43 (14.2)	
Microbiologically evaluable	Linezolid	143 (100)	126 (88.1)	17 (11.9)	0.606 (−5.6, 9.7 [2.0])
	Oxacillin-dicloxacillin	151 (100)	130 (86.1)	21 (13.9)	

[a] Percentages based on number of assessed patients.
[b] Confidence interval based on normal approximation, expressed as a percentage.
[c] Includes patients with missing or indeterminate outcomes.

oxacillin-dicloxacillin groups, respectively ($P = 0.024$; 95% CI, 1.2 to 16.5 [point estimate, 8.6]). In addition, no statistically significant differences in clinical cure rate were observed between treatment groups when analyzed by diagnosis.

In the microbiologically evaluable patients, the microbiological success rate at the TOC visit was similar between treatment groups, with 126 of 143 (88.1%) patients in the linezolid group and 130 of 151 (86.1%) patients in the oxacillin-dicloxacillin group achieving microbiological success ($P = 0.606$; 95% CI, −5.6 to 9.7 [point estimate, 2.0]). Subgroup analysis of microbiological outcome by gender, age, and race demonstrated comparable results between treatment groups. Eradication rates of selected baseline pathogens (*S. aureus, S. pyogenes*, and *S. agalactiae*) at the TOC visit are summarized for the microbiologically evaluable patients in Table 4. Eradication rates generally were similar between treatment groups for these pathogens. For *S. aureus*, the eradication rate in the linezolid group was 91.4% (85 of 93 patients) compared with 84.5% (87 of 103 patients) in the oxacillin-dicloxacillin group ($P = 0.139$; 95% CI, −2.1 to 16.0 [point estimate, 6.9]).

Consistent with the resolution of infection, a comparable improvement in clinical signs and symptoms of infection was observed from baseline to follow-up. At baseline, the incidences of moderate to severe swelling and/or induration were similar in both treatment groups (273 of 298 patients [91.6%] in the linezolid group and 279 of 301 patients [92.7%] in the oxacillin-dicloxacillin group). At the follow-up visit, the most common symptom of infection still present in clinically evaluable patients was swelling and/or induration, in 39 of 298 (13.1%) linezolid-treated patients and 53 of 302 (17.5%) oxacillin-dicloxacillin-treated patients, with moderate to severe swelling and/or induration reported in 3 patients in each treatment group. Mean changes in WBC count, absolute neutrophil count, and temperature during the study in both treatment groups also were consistent with the resolution of infection.

In the ITT population, less than 1% of all patients experienced reinfection, superinfections, or colonizations. Of the 400 linezolid-treated patients, none had a reinfection; superinfection was observed in 1 patient and colonization was observed in 2 patients. Of the 419 patients who received oxacillin-dicloxacillin, 1 had a reinfection, 2 had a superinfection, and 1 had colonization.

Safety. Safety assessments were performed on the ITT population. The frequencies of adverse events reported, regardless of causality, were comparable between treatment groups. A total of 47.3% (189 of 400) of the patients in the linezolid group and 41.3% (173 of 419) of the patients in the oxacillin-dicloxacillin treatment group experienced at least one adverse event. Frequencies of reported adverse events reported in ≥2% of patients in either treatment group are presented in Table 5. The most frequently reported adverse events in the linezolid group were nausea (23 of 400 patients [5.8%]), headache (22 of 400 patients [5.5%]), and vomiting (13 of 400 patients [3.3%]), while those most frequently reported in the oxacillin-dicloxacillin group were nausea (24 of 419 patients [5.7%]), headache (16 of 419 patients [3.8%]), and constipation (13 of 419 patients [3.1%]).

The percentages of patients with at least one adverse event considered to be drug related were similar between the linezolid and oxacillin-dicloxacillin groups (67 of 400 patients [16.8%] versus 72 of 419 patients [17.2 %], respectively). The most common drug-related adverse events in the linezolid group were nausea (14 of 400 patients [3.5%]) and headache (10 of 400 patients [2.5%]). Nausea (12 of 419 patients [2.9%]) was the most common drug-related adverse event in the oxacillin-dicloxacillin group. No statistically significant differences in the frequency of drug-related adverse events were observed between treatment groups. In addition, most drug-related adverse events reported in both treatment groups were characterized as mild or moderate in intensity.

Serious adverse events were reported in 5.5% (22 of 400) of linezolid-treated patients and in 4.5% (19 of 419) of oxacillin-dicloxacillin-treated patients. In the linezolid group, none was considered to be drug related, while four were considered possibly or probably drug-related in the oxacillin-dicloxacillin group. Death was reported in three linezolid-treated patients and in one oxacillin-dicloxacillin-treated patient; none of these was considered by the investigator to be drug related.

Hypertension was reported in 12 of 400 (3.0%) of linezolid-treated patients and 1 of 419 (0.2%) of oxacillin-dicloxacillin-

TABLE 4. Eradication rates of selected baseline pathogens[a]

Pathogen	Eradication rate (%)[b] with:		*P* (95% CI[c] [point estimate])
	Linezolid	Oxacillin-dicloxacillin	
S. aureus	85/93 (91.4)	87/103 (84.5)	0.139 (−2.1, 16.0 [6.9])
S. pyogenes	23/29 (79.3)	27/32 (84.4)	0.607 (−24.4, 14.3 [5.1])
S. agalactiae	7/7 (100)	4/6 (66.7)	0.097 (−4.4, 71.1 [33.3])

[a] In microbiologically evaluable patients.
[b] Eradication rate = number of eradicated pathogens divided by the total of eradicated and noneradicated pathogens.
[c] Confidence interval based on normal approximation, expressed as a percentage.

TABLE 5. Adverse events reported in ≥2% of patients in the ITT population

Adverse event	No. (%) of patients in treatment group	
	Linezolid (n = 400)	Oxacillin-dicloxacillin (n = 419)
Nausea	23 (5.8)	24 (5.7)
Headache	22 (5.5)	16 (3.8)
Vomiting	13 (3.3)	8 (1.9)
Hypertension	12 (3.0)	1 (0.2)
Diarrhea	11 (2.8)	12 (2.9)
Localized pain	11 (2.8)	3 (0.7)
Dyspepsia	10 (2.5)	7 (1.7)
Insomnia	10 (2.5)	9 (2.1)
Dizziness	9 (2.3)	3 (0.7)
Abdominal pain (localized)	8 (2.0)	5 (1.2)
Constipation	7 (1.8)	13 (3.1)
Pruritus (nonapplication site)	6 (1.5)	9 (2.1)
Fever	5 (1.3)	11 (2.6)

treated patients. Seven of the linezolid-treated patients had baseline hypertension, which was not adversely affected by the subsequent administration of linezolid. Four patients had normal baseline blood pressure measurements and intermittently elevated blood pressure measurements during treatment; three of these four had normal measurements at follow-up. One patient with no prior history of hypertension had a single isolated elevated (170/110 mm Hg) measurement on day 9 of treatment, but all other measurements were normal. Since linezolid is classified as a mild inhibitor of monoamine oxidase (MAO), an analysis was performed to examine a potential MAO interaction in these patients with hypertension. Eleven of these 12 patients were not on any concomitant medications that had MAO-interacting or -inhibitory properties, therefore decreasing the likelihood that this was attributable to MAO interaction. In addition, for all enrolled patients in the study who were not receiving a concomitant potent MAO inhibitor but receiving a MAO-interacting drug, there was no difference between linezolid-treated patients and oxacillin-dicloxacillin-treated patients in the change from baseline for mean systolic blood pressure, mean diastolic blood pressure, and mean arterial pressure.

Similar percentages of patients withdrew from the study due to adverse events in the linezolid group (12 of 400 patients [3.0%]) and the oxacillin-dicloxacillin group (23 of 419 patients [5.5%]). However, significantly more patients in the oxacillin-dicloxacillin group withdrew due to adverse events judged to be drug-related than did patients in the linezolid group (15 of 419 patients [3.6%] versus 4 of 400 [1.0%], respectively; P = 0.014).

No clinically relevant changes in physical examination observations, vital sign results, or hematological or clinical chemistry panels were observed from baseline to follow-up. No potential drug interactions between linezolid and MAO inhibitors or any other concomitant medications were observed.

DISCUSSION

This well-designed randomized trial compared the efficacy and safety of linezolid, a new oxazolidinone, with those of oxacillin-dicloxacillin, a therapy of choice in many parts of the world, for patients with complicated skin and soft tissue infections. Both treatment groups were similar with respect to their demographics, baseline infections, and evaluability of the patients. Results of this study indicated that linezolid is as effective as oxacillin-dicloxacillin in the treatment of these infections. Clinical cure rates and microbiological success rates for linezolid-treated patients were high (88.6 and 88.1%, respectively) and compared favorably with those observed in oxacillin-dicloxacillin-treated patients (85.8 and 86.1%, respectively). Linezolid also was as effective as oxacillin-dicloxacillin in eradicating *S. aureus, S. pyogenes,* and *S. agalactiae*. Most patients in both treatment groups were able to switch from i.v. to p.o. therapy (based on clinical improvement) within 5 days of therapy initiation, and 80% of patients completed both the treatment and follow-up phases of the study.

Gram-positive bacteria are important pathogens among patients with skin and soft tissue infections. Historically, oxacillin has been a drug of choice for many gram-positive skin and soft tissue infections (27). However, the emergence of multidrug-resistant gram-positive species, particularly MRSA, is an increasing concern; in recent surveys in the United States and Europe, methicillin resistance has been observed in 22 to 25% of *S. aureus* isolates from patients with skin and soft tissue infections (5, 13). Although patients with MRSA were excluded from this study, the increasing prevalence of resistant gram-positive pathogens suggests that many patients will require treatment with an antimicrobial that has activity against these resistant strains.

Linezolid may substantially impact the approach to treatment of skin and soft tissue infections caused by many gram-positive species because it has a unique mechanism of action, possesses significant activity against gram-positive pathogens (including MRSA), and has excellent clinical efficacy as demonstrated in this and other studies (6, 22). Thus, it is a promising empiric treatment for either community-acquired or nosocomial skin and soft tissue infections. Linezolid's efficacy in treating skin and soft tissue infections may be due, in part, to the high concentrations achieved in the skin (K. M. Donaldson, P. Blood., T. J. Parker, P. T. Daly-Yates, and J. D. Harry, unpublished data) and its ability to inhibit bacterial virulence factor and toxin production in *S. aureus* and *S. pyogenes* at concentrations well below the MICs (C. G. Gemmell and C. W. Ford, Abstr. 39th Intersci Conf. Antimicrob. Agents Chemother., abstr. 1537, 1994). It has been suggested that antimicrobials that have both antibacterial properties as well as the ability to inhibit the synthesis of bacterial toxins may provide greater efficacy and improved outcomes in these gram-positive bacterial toxin-mediated diseases (1, 24, 25).

Unlike other antibiotics, the oral formulation of linezolid is 100% bioequivalent to the intravenous formulation, ensuring that patients receive adequate serum and tissue concentrations of drug upon switch to oral therapy. This will allow physicians to switch to the oral formulation earlier in hospitalized patients and may result in earlier discharge (16). Further studies evaluating the use of oral linezolid alone in the treatment of complicated skin and soft tissue infections are needed.

In the present study, linezolid proved to be safe and well tolerated regardless of the site of infection. The majority of adverse events reported were mild or moderate in intensity. No serious drug-related adverse events were reported in the linezolid group. In addition, there was no evidence of a drug interaction between linezolid and MAO inhibitors or any other concomitant medications. Hypertension was reported in 3.0% of patients receiving linezolid; however, a direct causal relationship could not be determined. In addition, although linezolid may cause mild MAO inhibition (2, 7), the hypertension observed in this trial did not appear to be related to this property of the drug.

Complicated skin and soft tissue infections are a significant cause of morbidity and mortality in hospitalized patients. The

emergence of resistant pathogens has created the need for newer, more effective antimicrobial therapies, which can be given parenterally or p.o. In conclusion, linezolid is well tolerated and as effective as oxacillin-dicloxacillin for complicated skin and soft tissue infections, with the added advantages of convenient twice-daily dosing administered either i.v. or p.o.

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