

Treating Foot Infections in Diabetic Patients: A Randomized, Multicenter, Open-Label Trial of Linezolid versus Ampicillin-Sulbactam/ Amoxicillin-Clavulanate

Benjamin A. Lipsky,¹ Kamal Itani,² Carl Norden,³ and the Linezolid Diabetic Foot Infections Study Group^a

¹Antibiotic Research Clinic, Veterans' Affairs Puget Sound Health Care System, and Department of Medicine, University of Washington, Seattle, Washington; ²Department of General Surgery, Veterans' Affairs Medical Center, Houston, Texas; and ³Pfizer, Peapack, New Jersey

Foot infections in diabetic patients are predominantly caused by gram-positive cocci, many of which are now antibiotic resistant. Because linezolid is active against these pathogens, we compared the efficacy and safety of intravenous and oral formulations with that of intravenous ampicillin-sulbactam and intravenous and oral amoxicillin-clavulanate given for 7–28 days in a randomized, open-label, multicenter study of all types of foot infection in diabetic patients (ratio of linezolid to comparator drug recipients, 2:1). Among 371 patients, the clinical cure rates associated with linezolid and the comparators were statistically equivalent overall (81% vs. 71%, respectively) but were significantly higher for linezolid-treated patients with infected foot ulcers (81% vs. 68%; $P = .018$) and for patients without osteomyelitis (87% vs. 72%; $P = .003$). Cure rates were comparable for inpatients and outpatients and for both oral and intravenous formulations. Drug-related adverse events were significantly more common in the linezolid group, but they were generally mild and reversible. Linezolid was at least as effective as aminopenicillin/ β -lactamase inhibitors for treating foot infections in diabetic patients.

Foot infections and their sequelae cause substantial morbidity among diabetic patients. Most infections are mild to moderate in severity [1], but more-severe infection may lead to serious sequelae. Foot infections in diabetic patients (hereafter, “diabetic foot infections”)

are often accompanied by osteomyelitis [2], and they are the leading cause of diabetes-related hospitalization [3] and lower-extremity amputation in the United States [1, 4, 5].

Acute infections in patients who have not recently received antibiotic therapy are predominantly caused by aerobic gram-positive cocci, often as a monomicrobial infection [6]. Although chronic wounds tend to develop more-complex flora [7, 8], *Staphylococcus aureus*, either alone or as a component of a mixed infection, is the most important pathogen in diabetic foot infection [7]. The incidence of infection caused by antibiotic-resistant bacteria, particularly methicillin-resistant *S. aureus* (MRSA), is increasing worldwide [9, 10]. In patients with diabetic foot infections, isolation of MRSA is associated with previous antibiotic therapy and leads to worse clinical outcomes [11–15]. Thus, agents with extended activity against MRSA are needed for patients at risk. Whether an empirical antibiotic

Received 16 April 2003; accepted 17 August 2003; electronically published 9 December 2003.

Presented in part: 40th Annual Meeting of the Infectious Diseases Society of America, Chicago, October 2002 (abstract 189).

Financial support: Pharmacia Corporation and Department of Veterans Affairs.

Financial disclosure: B.A.L. and K.I. have received research support from, served as advisors to, and served as speakers for Pharmacia (now Pfizer). C.N. is an employee of Pfizer (formerly Pharmacia).

^a Members of the study group are listed after the text.

Reprints or correspondence: Dr. Benjamin A. Lipsky, Dept. of Medicine, University of Washington, Veterans' Affairs Puget Sound Health Care System (S-111-GIMC), 1660 S. Columbian Wy., Seattle, WA 98108-1597 (Benjamin.Lipsky@med.va.gov).

Clinical Infectious Diseases 2004;38:17–24

© 2004 by the Infectious Diseases Society of America. All rights reserved.
1058-4838/2004/3801-0003\$15.00

regimen for diabetic foot infection must also be effective against gram-negative bacilli and anaerobes is not clear, but one previous study suggested that it might not be necessary [6]. The work of Lipsky et al. [6] and other studies [16, 17] also suggest that therapy with oral antimicrobial agents is effective, but few studies have compared the outcomes of oral and parenteral regimens.

Linezolid is effective for treatment of infections due to gram-positive bacteria, including methicillin-, cephalosporin-, and vancomycin-resistant strains [18–21], but it has minimal activity against gram-negative bacteria. It is available in both a parenteral and a highly bioavailable oral formulation, is administered twice per day, and achieves therapeutic concentrations in soft tissue and bone [22, 23]. However, linezolid is expensive, and some clinicians prefer to reserve it for treatment of documented antibiotic-resistant organisms. The aminopenicillin/ β -lactamase inhibitors ampicillin-sulbactam and amoxicillin-clavulanate are broad-spectrum antibiotics that are among the most widely used agents for these infections [24]. This study compared the efficacy and safety of intravenous and oral formulations of linezolid with that of aminopenicillin/ β -lactamase inhibitors (plus vancomycin, if needed for MRSA) for treatment of patients with various types of diabetic foot infection.

PATIENTS AND METHODS

Study design. This randomized, open-label trial was conducted at 45 sites in 8 countries from April 2001 through April 2002. Consenting men and women (age, ≥ 18 years) with diabetes mellitus (diagnosed on the basis of the American Diabetes Association's definition) [25] and a foot infection were potentially eligible. Infections were defined by clinical signs and symptoms (see below) and comprised ≥ 1 of the following: cellulitis, paronychia, infected ulcer, deep soft-tissue infection, septic arthritis, abscess, or osteomyelitis. Patients could have undergone any necessary debridement or other surgical procedures, as long as the entire infected area was not resected or amputated. At each study site, appropriate informed consent was obtained, and guidelines for human experimentation (as defined by the US Department of Health and Human Services or the investigators' institution) were followed in the conduct of this clinical trial.

Patients were excluded from the study if they had critical ischemia of the affected limb (defined as the absence of pedal pulses, absent or abnormal Doppler wave forms, and a toe blood pressure of <45 mm Hg), unless their participation was approved by a vascular surgeon; if they had a wound with prosthetic materials or devices; if they had an infection requiring >28 days of antibiotic treatment; or if they had a wound with extensive gangrene. Patients were also excluded if they had

received potentially effective antibiotic therapy for >72 h in the week before enrollment, if they needed additional treatment with antibiotics not tested in our study, if they had an absolute neutrophil count of <500 cells/mm³, if they were pregnant or lactating, or if they had a history of hypersensitivity to linezolid, penicillin, or vancomycin.

At enrollment, each patient provided a medical history and underwent a physical examination. The infection site was assessed for drainage, erythema, fluctuance, warmth, pain or tenderness, and induration. The area and depth of the wound were measured, and the condition of the ulcer base and surrounding skin were noted. The affected foot was assessed for the presence of ischemia and osteomyelitis. Each patient underwent plain radiography of the affected limb and standard hematological and clinical chemistry testing. Patients suspected of having osteomyelitis underwent whatever additional studies (e.g., imaging tests or bone biopsy) were deemed appropriate by the investigators, who also based the diagnosis on these results. Osteomyelitis frequently complicates diabetic foot infection and is difficult to exclude in the early stages; furthermore, the optimal duration of therapy it requires is unclear. We allowed patients with presumed osteomyelitis to be enrolled if the investigator believed 4 weeks of antibiotic therapy was sufficient for treatment. For each patient, we obtained the clinical history, performed a physical examination and detailed wound assessment, and obtained specified laboratory tests periodically throughout the study, at the end of treatment, and during follow-up. Plain radiography was repeated 7–14 days after the start of therapy.

Wounds with callus or necrotic material were sharply debrided. Then, suitable tissue wound specimens were obtained for bacterial cultures (aerobic and anaerobic) within 72 h after enrollment (i.e., at baseline); cultures were done at the investigators' laboratory. Open wound specimens for culture were obtained by biopsy or curettage (usually with a sterile scalpel) of tissue at the base of the wound; obtaining swab specimens was discouraged for cultures. Fine-needle aspiration or biopsy was recommended for closed lesions or cellulitis. Patients with suspected bacteremia had ≥ 2 blood specimens obtained for culture. If appropriate wound specimens were available or if bacteremia was documented, cultures were repeated 48–72 h after the initiation of therapy, at the end of treatment, and during follow-up. Patients were withdrawn from the study if a culture yielded a pathogen that was resistant to a study medication and the infection was not clinically improving, if the absolute neutrophil count was <500 cells/mm³, if the infection was failing to improve, if the patient did not comply with the study regimen, or if the patient had persistent bacteremia (i.e., 3 consecutive positive blood culture results) without clinical improvement. The test-of-cure evaluation was conducted 15–21 days after treatment was completed.

Patients were randomized (ratio, 2:1) to receive either linezolid (600 mg q12 h either iv or po), ampicillin-sulbactam (1.5–3 g q6h iv), or amoxicillin-clavulanate (500–875 mg every 8–12 h po). At the investigator’s discretion, therapy could be given on an inpatient or outpatient basis, could be administered either intravenously or orally, and could be switched from the intravenous to oral administration. The duration of treatment was ≥ 7 days but not > 28 days. Vancomycin (1 g q12h iv, adjusted for renal dysfunction, advanced age, or obesity) was to be added to the aminopenicillin/ β -lactamase inhibitor regimen if infection with MRSA was suspected or confirmed. The investigator could choose to administer aztreonam (1–2 g iv every 8–12 h in either arm) for patients infected with suspected or documented gram-negative pathogens that were resistant to the study medication.

To avoid confusion about the effect of the study antibiotic, use of topical antimicrobial agents was not permitted. Patients received twice-daily dressing changes (which consisted of any sterile nonadherent type selected by the investigator) and periodic debridement, as needed throughout the study. Pressure on the wound had to be avoided by a method selected by the investigator.

Analysis of results. Analyses were based on the intent-to-treat (ITT) population (i.e., evaluable randomized patients who received ≥ 1 dose of study medication). Analysis of the clinical outcome associated with the infecting pathogen at baseline involved the modified intent-to-treat population (i.e., ITT patients with a gram-positive baseline pathogen). The primary efficacy outcome was the clinical response to treatment, both overall and by type of infection, at the test-of-cure visit. Clinical outcomes were categorized as follows: “cure,” resolution of all clinical signs and symptoms of infection and a healing wound after ≥ 5 days of therapy; “improvement,” resolution of ≥ 2 —but not all—clinical signs or symptoms of infection after ≥ 5 days of therapy (only used at end of treatment); “failure,” persistence or progression of baseline clinical signs and symptoms of infection after ≥ 2 days of therapy; “missing,” patients received therapy for < 2 days; or “indeterminate,” circumstances precluded classification. All patients who received ≥ 1 dose of study medication were included in the safety analyses.

Statistical analyses. The significance level was set at 5% ($P \leq .05$), as determined using SAS software, version 6.12 (SAS Institute). Comparability of treatment groups for quantitative variables used a 1-way analysis of variance fixed-effects model, with treatment group as a categorical factor, or the Wilcoxon rank sum test. Comparability between treatment groups for categorical variables was determined using the χ^2 test for homogeneity of proportions or Fisher’s exact test. The efficacy analyses used 2-sided 95% CIs based on normal approximation to the binomial distribution of success or failure. Summaries of categorical variables included the frequencies and percent-

ages of patients within each category. Continuous variables were summarized using descriptive statistics.

RESULTS

Study population. Of the 371 patients enrolled, 241 received linezolid, 120 received aminopenicillin/ β -lactamase inhibitors, and 10 received no treatment. Clinically evaluable patients met entry criteria, received $\geq 80\%$ of prescribed study medication, and had adequate follow-up; there were 203 patients in the linezolid group and 108 patients in the aminopenicillin/ β -lactamase inhibitor groups.

There were no significant differences between the 2 treatment groups at baseline with respect to demographic characteristics (table 1), medical histories, findings of physical examination, and results of laboratory tests. The most common types of infections are shown in table 1. Investigators diagnosed osteomyelitis in 77 patients; 64 of these patients had characteristic radiographic changes (3 of whom also had a positive radionuclide scan or MRI result, and 9 of whom had a positive result of culture of a bone biopsy specimen), 7 had only a positive bone biopsy culture result, and 6 had only a positive radionuclide scan or MRI result. Fifty-seven patients with osteomyelitis received linezolid, and 20 received aminopenicillin/ β -lactamase inhibitors. Foot ischemia was noted in 147 enrolled patients, 98 of whom received linezolid and 49 of whom received aminopenicillin/ β -lactamase inhibitors. The most com-

Table 1. Baseline demographic and clinical characteristics of the intent-to-treat population.

Characteristic	Linezolid arm (n = 241)	Aminopenicillin/ β -lactamase inhibitor arms (n = 120)
Demographic		
Male sex	171 (71)	86 (72)
Race		
White	206 (85)	100 (83)
Black	27 (11)	16 (13)
Other	8 (3)	4 (3)
Age, mean years \pm SD	63 \pm 12	62 \pm 13
Type-2 diabetes, % of patients	61	52
Type of infection ^a		
Infected ulcer	190 (79)	93 (78)
Cellulitis	101 (42)	60 (50)
Deep soft-tissue infection	37 (15)	16 (13)
Paronychia	12 (5)	11 (9)
Osteomyelitis	57 (24)	20 (17)
Other	8 (3)	5 (4)

NOTE. Data are no. (%) of patients, unless otherwise indicated.

^a Patients could have had > 1 type of or site of infection. Therefore, the sum of the percentages may be $> 100\%$.

Table 2. Clinical cure rates for the intent-to-treat population, by selected parameters.

Parameter	No. of patients cured/ no. of patients assessed (%) ^a		95% CI	Duration of therapy, mean days \pm SD
	Linezolid arm (n = 241)	Aminopenicillin/ β -lactamase inhibitor arms (n = 120)		
Overall	165/203 (81)	77/108 (71)	-0.1 to 20.1	17.0 \pm 7.6
Type of infection ^b				
Infected ulcer	131/161 (81)	57/84 (68)	1.9–25.2	17.0 \pm 7.5
Cellulitis	68/86 (79)	40/54 (74)	-9.5 to 19.5	17.1 \pm 7.9
Deep soft-tissue infection	20/32 (63)	8/14 (57)	-25.5 to 36.2	20.2 \pm 7.5
Paronychia	11/12 (92)	9/11 (82)	-17.8 to 37.5	15.1 \pm 6.5
Abscess	5/5 (100)	1/1 (100)	...	14.3 \pm 6.2
Osteomyelitis ^c	27/44 (61)	11/16 (69)	-34.3 to 19.5	19.0 \pm 9.0
Status during initial treatment				
Outpatient	110/134 (82)	57/79 (72)	-1.9 to 21.8	16.0 \pm 7.3
Inpatient	55/69 (80)	20/29 (69)	-8.6 to 30.1	19.2 \pm 7.8
Route of initial treatment				
Intravenous	41/53 (77)	15/22 (68)	-13.3 to 31.7	20.7 \pm 7.6
Oral	124/150 (83)	62/86 (72)	-0.7 to 21.8	15.8 \pm 7.2
Presence of ischemia ^c				
Yes	64/79 (81)	29/44 (66)	-1.4 to 31.6	18.2 \pm 7.8
No	101/124 (81)	48/64 (75)	-6.2 to 19.1	16.2 \pm 7.4

^a Excludes patients with indeterminate and missing outcomes.

^b Patients could have had >1 baseline diagnosis.

^c See text for definitions.

mon site of infection was the plantar surface (47%), followed by the dorsal aspect of the foot (28%).

There were no significant differences in wound characteristics between the 2 treatment groups: most wounds were ≤ 2 cm² in size and ≤ 9 mm deep and were present for a duration of <8 weeks. Clinical characteristics of the infected sites were similar in the treatment groups at baseline. The organisms isolated from wound cultures were similar for the treatment groups. Overall, one-half of all patients had only gram-positive cocci isolated. The most common individual pathogens at baseline were *S. aureus* (158 isolates), *Staphylococcus epidermidis* and other coagulase-negative staphylococci (60 isolates), *Enterococcus* species (59 isolates), and *Streptococcus agalactiae* (52 isolates). In the linezolid group, 70 patients (45%) were infected with only gram-positive aerobic pathogens, 5 (3%) were infected with a gram-positive pathogen plus an obligate anaerobe, and 81 (52%) had mixed infections with gram-positive and gram-negative pathogens. In the aminopenicillin/ β -lactamase inhibitors group, 50 patients (58%) were infected with only a gram-positive pathogen, 2 (2%) were infected with a gram-positive pathogen and an anaerobe, and 34 patients (40%) were infected with both gram-positive and gram-negative pathogens.

Mean total treatment duration (\pm SD) was similar in the

linezolid (17.2 \pm 7.9 days) and aminopenicillin/ β -lactamase inhibitor (16.5 \pm 7.9 days) groups. Intravenous treatment duration was shorter for patients treated with linezolid than for those treated with aminopenicillin/ β -lactamase inhibitors (7.8 \pm 5.5 vs. 10.4 \pm 5.7 days, respectively), whereas durations of oral treatment were similar (15.9 \pm 7.4 and 15.0 \pm 7.8 days, respectively). Vancomycin was administered to 1 patient (0.4%) in the linezolid group (a protocol violation) and to 5 patients (9.6%) in the aminopenicillin/ β -lactamase inhibitor groups. Aztreonam was administered to 12 linezolid recipients (5.0%) and to 3 aminopenicillin/ β -lactamase inhibitor recipients (2.5%).

Efficacy data. There was no statistically significant difference between the treatment groups in the overall clinical cure rate (table 2). When analyzed by primary diagnosis, however, statistically significantly more patients with an infected ulcer (78% of all patients) in the linezolid arm were clinically cured than in the aminopenicillin/ β -lactamase inhibitor arm (81% vs. 68%, respectively; 95% CI, 1.9–25.2; $P = .018$). Similarly, among the 79% of patients who did not have osteomyelitis, those treated with linezolid had a statistically significantly higher cure rate than did those receiving aminopenicillin/ β -lactamase inhibitors (87% vs. 72%; 95% CI, 4.5–25.7; $P =$

Table 3. Clinical cure rates for infections with the most frequently isolated baseline pathogens in the modified intent-to-treat population.

Pathogen	No. of patients cured/ no. of patients assessed (%) ^a			Baseline organism isolated at follow-up ^a , no. of patients	
	Linezolid arm	Aminopenicillin/ β -lactamase inhibitor arms	95% CI	Linezolid arm	Aminopenicillin/ β -lactamase inhibitor arms
<i>Staphylococcus aureus</i>					
Methicillin susceptible	50/67 (75)	28/39 (72)	-14.7 to 20.4	5	4
Methicillin resistant	13/18 (72)	4/7 (57) ^b	-27.0 to 57.2	3	0
Coagulase-negative staphylococci	31/35 (89)	17/19 (89)	-18.3 to 16.5	2	1
<i>Streptococcus agalactiae</i>	26/31 (84)	9/18 (50)	7.4-60.4	0	1
<i>Enterococcus</i> species ^c	23/34 (68)	13/17 (76)	-34.4 to 16.8	1	1
<i>Pseudomonas</i> species ^d	13/16 (81)	7/11 (64)	-16.6 to 51.9	3	0
Enterobacteriaceae ^d	52/65 (80)	16/23 (70)	-10.7 to 31.6	2	1

NOTE. The modified intent-to-treat population consisted of patients in the intent-to-treat population with a baseline pathogen and evaluable clinical response of success or failure).

^a Patient was considered to be a clinical success even if the organism was isolated at follow-up.

^b Four of the 7 patients received vancomycin, 3 of whom were clinically cured. One patient who was clinically cured did not receive vancomycin.

^c Only 1 of the tested *Enterococcus* isolates was resistant to vancomycin.

^d Gram-negative organisms were isolated in conjunction with gram-positive pathogens.

.003). Clinical outcomes were similar between treatment groups among patients with cellulitis, deep soft-tissue infection, paronychia, abscess, and osteomyelitis. Rates of cure were generally lower in both treatment arms for deep soft-tissue infection and bone infection (~60% to 65%) than for more superficial infections (~75% to 80%). There were no significant differences in clinical cure rates between patients treated as inpatients and those treated as outpatients (for linezolid, 80% vs. 82%, respectively; for aminopenicillin/ β -lactamase inhibitors, 69% vs. 75%, respectively), for initial intravenous therapy versus oral therapy (for linezolid, 77% vs. 83%, respectively; for aminopenicillin/ β -lactamase inhibitors, 68% vs. 72%, respectively), or for noncritical limb ischemia versus absence of critical limb ischemia (for linezolid, 81% vs. 81%, respectively; for aminopenicillin/ β -lactamase inhibitors, 66% vs. 75%, respectively) (table 2).

Clinical cure rates among patients whose cultures yielded only gram-positive organisms—with or without anaerobes—were 79% for the linezolid group (59 of 75 patients) and 73% for the aminopenicillin/ β -lactamase inhibitor groups (38 of 52 patients; 95% CI, -9.6 to 20.8). Clinical cure rates among patients infected with both gram-positive and gram-negative organisms who received aztreonam (in addition to the study drug) were 80% (8 of 10 patients) and 0% (0 of 3 patients) for the linezolid and aminopenicillin/ β -lactamase inhibitor groups, respectively (95% CI, 55.2-100); corresponding cure rates for those who did not receive aztreonam were 80% (57 of 71 patients) and 74% (23 of 31 patients). The clinical cure

rates, by baseline pathogen, were similar for the treatment groups, except that the rate of clinical cure was significantly higher among linezolid recipients infected with *S. agalactiae* (table 3). No isolated gram-positive pathogen was resistant to linezolid at baseline, nor did resistance develop in any patients during therapy. Resistance to ampicillin-sulbactam was documented for 8 *S. aureus* isolates and 4 coagulase-negative staphylococcal isolates.

Safety data. Treatment-related adverse events occurred in 55% and 53% of patients in the linezolid and aminopenicillin/ β -lactamase inhibitor groups, respectively ($P = .82$). Events were generally mild to moderate in intensity and of limited duration. Overall, significantly fewer patients experienced a drug-related adverse event in the aminopenicillin/ β -lactamase inhibitor groups than in the linezolid group (12 [10%] of 120 patients vs. 64 [27%] of 241 patients, respectively; $P = .001$), but the frequencies of drug-related events leading to drug discontinuation were comparable (4 [3%] of 120 patients vs. 18 [8%] of 241 patients, respectively; $P = .16$) (table 4). The significantly more common linezolid-related adverse events were nausea (5.8% of patients), anemia (5%), and thrombocytopenia (4%); these were mild to moderate in intensity in all but 1 patient (who had a nadir hemoglobin concentration of 7.2 g/dL and who recovered) and resolved in all but 1 patient (who died of causes unrelated to linezolid therapy). The mean duration of linezolid therapy (\pm SD) in patients who developed anemia was 21 ± 8 days (median, 25 days), and 93% of patients received linezolid for ≥ 14 days (overall, 67% of patients re-

Table 4. Drug-related adverse events.

Adverse event	Linezolid arm (n = 241)		Aminopenicillin/ β -lactamase inhibitor arms (n = 120)		P ^c
	No. (%) of patients ^a	No. of patients who discontinued therapy ^b	No. (%) of patients ^a	No. of patients who discontinued therapy ^b	
Any event	64 (26.6)	18	12 (10.0)	4	<.001
Diarrhea	18 (7.5)	5	4 (3.3)	1	.162
Nausea	14 (5.8)	4	0 (0)	0	.006
Anemia	11 (4.6)	2	0 (0)	0	.019
Thrombocytopenia	9 (3.7)	3	0 (0)	0	.032
Vomiting	4 (1.7)	3	1 (0.8)	0	>.999
Decreased appetite	3 (1.2)	0	0 (0)	0	.554
Dyspepsia	3 (1.2)	1	1 (0.8)	0	>.999

^a Percentages are based on the number of patients reporting the event for each treatment arm.

^b Patients for whom therapy was discontinued because of adverse event(s).

^c P values refer to the differences between the number of adverse events.

ceived linezolid for ≥ 14 days). Platelet counts decreased to $<100,000$ platelets/mm³ and decreased by $\geq 25,000$ platelets/mm³ in 9 (6%) of 145 patients who received linezolid therapy for >14 days and in 4 (4%) of 94 patients who received it for ≤ 14 days. One patient in the linezolid arm with anemia had gastrointestinal bleeding but subsequently recovered. Changes from baseline and abnormal clinical values for serum chemistry and urinalysis studies were similar between treatment groups.

DISCUSSION

Many organisms may cause foot infections in diabetic patients, but aerobic gram-positive cocci are the most frequent and virulent pathogens [6, 11–15]. Thus, therapy for these infections requires an antibiotic active against staphylococci and streptococci. The increasing prevalence of antibiotic resistance among these species (especially MRSA) is disconcerting, because infections with these organisms may have a worse outcome and necessitate selecting from a smaller group of antibiotics [12, 14]. Traditionally, diabetic foot infections have been treated intravenously to assure adequate antibiotic concentrations, especially in patients with severe infection or peripheral vascular disease [8, 26]. Newer agents (e.g., linezolid and the fluoroquinolones) with therapeutically equivalent intravenous and oral formulations allow initial treatment to be oral for persons who are clinically stable and allow an early switch from intravenous to oral antibiotics for those who are responding to therapy [27].

The few previous antibiotic trials of diabetic foot infections have differed in their designs, drug regimens, efficacy end points, and types and severities of infections included, making their results difficult to compare [8, 28]. Overall, however, outcomes with various antibiotics have been similar, with no one

drug or combination being superior [8]. To our knowledge, this randomized, controlled study is the largest published trial of the outcome of treating diabetic foot infections, the first to enroll patients in several countries, and one of the few to have enrolled patients with the full spectrum of infection severity. The design was also unique in allowing enrollment of patients with almost all types of infections, inpatient or outpatient treatment, and oral or parenteral therapy. We analyzed the outcomes for patients on the basis of variables selected in advance. Allowing use of aztreonam for treatment of infection with gram-negative pathogens in both arms and vancomycin for treatment of MRSA in the aminopenicillin/ β -lactamase inhibitor arm was another unique element.

The overall cure rates in this study (almost two-thirds of patients with deep or bone infections and more than three-quarters of patients with more superficial infections were cured) were comparable to those in most other studies of diabetic foot infections [8]. It is surprising that, because this trial was powered only to demonstrate equivalence of the regimens, linezolid recipients had statistically significantly better clinical cure rates than did aminopenicillin/ β -lactamase inhibitor recipients for the largest subsets of infection types (i.e., patients with an infected ulcer [81% vs. 68%] and patients without osteomyelitis [87% vs. 72%]). Clinical cure rates for the 2 treatment arms were comparable for the other infection types. As shown in other studies [2, 29, 30], cure rates were lower for patients with osteomyelitis, but they were comparable for the 2 treatment groups (61% and 69% for linezolid and aminopenicillin/ β -lactamase inhibitor groups, respectively). This may have resulted from the shorter duration of therapy (mean duration, 18 ± 9 days) for patients with osteomyelitis than is commonly recommended [2]. Because osteomyelitis is a chronic infection for these patients, long-term follow-up would be needed to

determine whether the remissions represented enduring cure. Although they were not primary end points in our study, cure rates were similar for patients with and patients without non-critical limb ischemia, for inpatients and outpatients, and for parenteral therapy and oral therapy recipients.

Linezolid was associated with more drug-related adverse events (mostly gastrointestinal and hematologic events) than were aminopenicillin/the β -lactamase inhibitors, but most of these events were mild, reversible, and did not require drug discontinuation. Anemia and thrombocytopenia associated with linezolid therapy were related to the duration of therapy, supporting the recommendation that weekly blood cell counts be determined if the duration of therapy exceeds 14 days.

This study demonstrates that therapy with linezolid is at least as effective as aminopenicillin and β -lactamase inhibitors (plus vancomycin for treatment of MRSA), the most frequently used agents [24] among patients with various types of diabetic foot infections. Among linezolid-treated patients infected with both gram-positive and gram-negative pathogens, clinical success rates were similar regardless of whether aztreonam was added to the treatment regimen, supporting the concept that addressing the primary gram-positive pathogens is most important. Empirical therapy, especially for patients with more-severe infections, should usually be broad-spectrum, pending culture results. There is less clinical experience with linezolid, and it was associated with more adverse effects; however, it has excellent pharmacokinetic properties and offers additional coverage against drug-resistant gram-positive organisms. Linezolid would be appropriate to consider for patients with diabetic foot infections that are known or suspected to be caused by MRSA. Our results also demonstrate that oral antibiotic therapy given in an outpatient setting can yield excellent results, even for patients with (noncritical) foot ischemia. These results are likely to be widely generalizable, because patients with a wide variety of infections (albeit mostly of mild to moderate severity) from many study sites in varied settings were enrolled.

THE LINEZOLID DIABETIC FOOT INFECTION STUDY GROUP PRINCIPAL INVESTIGATORS

K. Van Acker, Universitair Ziekenhuis Antwerpen, Diabetische voetkliniek, Belgium; K. Lagey, Academisch Ziekenhuis van de Vrije Universiteit Brussels, Diabetische voetkliniek, Belgium; G. Fierlbeck, Universitaesklinikum Tuebingen, Hautklinik, Germany; H. Rietzsch, Universitaetklinikum Carl Gustav Carus, Medizinische Klinik III, Germany; B. Amann, Staedtsche Kliniken Dortmund, Medizinische Klinik Nord, Germany; H.R. Ochs, Marienkrankenhaus, Abteilung fur Innere Medizin, Germany; F. DeLalla, U.O. Malattie Infettive, Ospedale S. Bortolo, Italy; F. Paradisi, Clinica Malattie Infettive, Universita degit Studi di Firenze, Italy; N. Candeias, Associacao Protectora dos

Diabeticos de Portugal, Portugal; B. Serra, Serv Endocrinologia, Hospital Geral de Santo Antonio, Portugal; J.M. Callejas, Vascular Surgery Service, Hospital German Trias I Pujol, Spain; R. Gomis, Endocrinology Service, Hospital Clinic de Barcelona, Spain; M. Cardona, Vascular Surgery, Hospital de la Creu Roja de Barcelona, Spain; C. Cuesta, Vascular Surgery Service, Hospital Ramon y Cajal, Spain; F. Acin, Vascular Surgery Service, Hospital de Getafe, Spain; J. Barberan, Infectious Disease Service, Hospital Gomez Ulla, Spain; M. Szenté Varga, Department for Heart and Vascular Surgery, University Hospital of Zurich, Switzerland; I. Baumgartner, Jolanda Voegelé, Switzerland; H. Vanniasinkam, Leeds General Infirmary, UK; M. Dryden, Microbiology Department, Royal Hampshire County Hospital, UK; B. Lipsky, VA Puget Sound Healthcare System, Seattle, WA; P. Sioson, Division of Infectious Disease, Jackson-Madison County General Hospital, Jackson, TN; P. Brachman, Piedmont Hospital, Atlanta Infectious Disease Group, Atlanta, GA; J. Mader, University of Texas Medical Branch, Galveston, TX; J.S. Tuber, Sun Valley Arthritis Center, Glendale, AZ; R. Chadband, Alabama Clinical Therapeutics, Birmingham, AL; V. Driver, Madigan Army Medical Center, Tacoma, WA; S. Jankauskas, SMO-USA, Inc., Longwood, FL; A. Kivitz, Bon Secours Holy Family Hospital, Regional Center for Ankle & Foot Care, Altoona, PA; R. Ramirez, University Community Hospital, Tamarac, FL; P. Forman, Staten Island University Hospital, Staten Island, NY; A. Landsman, Grant Hospital, Holy Family Hospital, Illinois Center for Clinical Research, Chicago, IL; A. Karchmer, Beth Israel/Deaconess Medical Center, Harvard Medical School, Boston, MA; K. Itani, Department of Surgery, Houston VA, Houston, TX; P. Blume, New Haven, CT; P. Chandraskar, Division of Infectious Diseases, Harper Hospital, Detroit, MI; D. Armstrong, Southern Arizona Veterans Affairs Medical Center, Tucson, AZ; S. Shaw, Rancho Los Amigos, National Rehabilitation Center, Los Angeles, CA; D. Hoyt, Wound Clinic at Regional Burn Center, UCSD Medical Center, San Diego, CA; L. Goldstein, Alameda County Hospital, Oakland, CA; M. Moursi, McClellan VA Hospital, Little Rock, AR; K.R. Reber, Dixie Regional Medical Center, St. George, UT; W.H. Davis, Miller Orthopedic Clinic, Charlotte, NC; L. Yonehiro, Baptist Hospital Wound Center, Pensacola, FL; and T. Lee, OSU Department of Orthopedics, Orthopedic Foot & Ankle Center, Columbus, OH.

Acknowledgment

We thank Bobbie Lee, M.Sc., for her biostatistical help.

References

1. Lipsky BA. Infectious problems of the foot in diabetic patients. In: JH Bowker, MA Pfeifer, eds. *The diabetic foot*. 6th ed. St. Louis, MO: Mosby, 2001:467–80.

2. Lipsky BA. Osteomyelitis of the foot in diabetic patients. *Clin Infect Dis* **1997**; 25:1318–26.
3. Smith DM, Weinberger M, Katz BP. Predicting nonelective hospitalization: a model based on risk factors associated with diabetes mellitus. *J Gen Intern Med* **1987**; 2:168–73.
4. Reiber GE. Epidemiology of foot ulcers and amputations in the diabetic foot. In: JH Bowker, MA Pfeifer, eds. *The diabetic foot*. 6th ed. St. Louis, MO: Mosby, **2001**:13–32.
5. Currie CJ, Morgan CL, Peters JR. The epidemiology and cost of inpatient care for peripheral vascular disease, infection, neuropathy, and ulceration in diabetes. *Diabetes Care* **1998**; 21:42–8.
6. Lipsky BA, Pecoraro RE, Larson SA, Hanley ME, Ahroni JH. Outpatient management of uncomplicated lower-extremity infections in diabetic patients. *Arch Intern Med* **1990**; 150:790–7.
7. Lipsky BA, Pecoraro RE, Wheat LJ. The diabetic foot: soft tissue and bone infection. *Infect Dis Clin North Am* **1990**; 4:409–32.
8. Lipsky BA. Evidence-based antibiotic therapy of diabetic foot infections. *FEMS Immunol Med Microbiol* **1999**; 26:267–76.
9. Fluckiger U, Widmer AF. Epidemiology of methicillin-resistant *Staphylococcus aureus*. *Chemotherapy* **1999**; 45:121–34.
10. Maranan MC, Moreira B, Boyle-Vavra S, Daum RS. Antimicrobial resistance in staphylococci: epidemiology, molecular mechanisms, and clinical relevance. *Infect Dis Clin North Am* **1997**; 11:813–49.
11. Tentolouris N, Jude EB, Smirnof I, Knowles EA, Boulton AJM. Methicillin-resistant *Staphylococcus aureus*: an increasing problem in a diabetic foot clinic. *Diabet Med* **1999**; 16:767–71.
12. Mantey I, Hill RL, Foster AV, Wilson S, Wade JJ, Edmonds ME. Infection of foot ulcers with *Staphylococcus aureus* associated with increase mortality in diabetic patients. *Commun Dis Public Health* **2000**; 3:288–90.
13. Wagner A, Reike H, Angelkort B. Highly resistant pathogens in patients with diabetic foot syndrome with special reference to methicillin-resistant *Staphylococcus aureus* infections [in German]. *Dtsch Med Wochenschr* **2001**; 126:1353–6.
14. Fejfarová V, Jirkovská A, Skibová J, Petkov V. Pathogen resistance and other risk factors in the frequency of lower limb amputations in patients with the diabetic foot syndrome [in Czech]. *Vnitr Lek* **2002**; 48:302–6.
15. Dang CN, Prasad YD, Boulton AW, Jude EB. Methicillin-resistant *Staphylococcus aureus* in the diabetic foot clinic: a worsening problem. *Diabet Med* **2003**; 20:159–61.
16. Sesin GP, Paszko A, O'Keefe E. Oral clindamycin and ciprofloxacin therapy for diabetic foot infections. *Pharmacotherapy* **1990**; 10:154–6.
17. Peterson LR, Lissack LM, Canter K, Fasching CE, Clabots C, Gerding DN. Therapy of lower extremity infections with ciprofloxacin in patients with diabetes mellitus, peripheral vascular disease, or both. *Am J Med* **1989**; 86:801–8.
18. Rubinstein E, Cammarata SK, Oliphant TH, Wunderink RG. Linezolid (PNU-100766) versus vancomycin in the treatment of hospitalized patients with nosocomial pneumonia: a randomized, double-blind, multicenter study. Linezolid Nosocomial Pneumonia Study Group. *Clin Infect Dis* **2001**; 32:402–12.
19. Stevens DL, Smith LG, Bruss JB, et al. Randomized comparison of linezolid (PNU-100766) versus oxacillin-dicloxacillin for treatment of complicated skin and soft tissue infections. Linezolid Skin and Soft Tissue Infections Study Group. *Antimicrob Agents Chemother* **2000**; 44:3408–13.
20. Stevens DL, Herr D, Lampiris H, Hunt JL, Batts DH, Hafkin B. Linezolid versus vancomycin for the treatment of methicillin-resistant *Staphylococcus aureus* infections. Linezolid MRSA Study Group. *Clin Infect Dis* **2002**; 34:1481–90.
21. Zurenko GE, Yagi BH, Schaadt RD, et al. In vitro activities of U-100592 and U-100766, novel oxazolidinone antibacterial agents. *Antimicrob Agents Chemother* **1996**; 40:839–45.
22. Lovering AM, Zhang J, Bannister GC, et al. Penetration of linezolid into bone, fat, muscle and haematoma of patients undergoing routine hip replacement. *J Antimicrob Chemother* **2002**; 50:73–7.
23. Rana B, Butcher I, Grigoris P, Murnaghan C, Seaton RA, Tobin CM. Linezolid penetration into osteo-articular tissues. *J Antimicrob Chemother* **2002**; 50:747–50.
24. Arlington Medical Resources (AMR). *The US hospital anti-infective market guide (USA and Europe editions)*. Malvern, PA: AMR, **2003**. Available at: <http://www.amr-data.com>. Accessed March 2002.
25. Report on the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus. *Diabetes Care* **2002**; 25(Suppl 1):S5–20.
26. West NJ. Systemic antimicrobial treatment of foot infections in diabetic patients. *Am J Health Syst Pharm* **1995**; 52:1199–207.
27. Ramirez JA. Managing anti-infective therapy of community-acquired pneumonia in the hospital setting: focus on switch therapy. *Pharmacotherapy* **2001**; 21:79S–82S.
28. Mason J, O'Keefe C, Hutchinson A, McIntosh A, Young R, Booth A. A systemic review of foot ulcer in patients with type 2 diabetes mellitus. II. Treatment. *Diabet Med* **1999**; 16:889–909.
29. Eneroth M, Apelqvist J, Stenstrom A. Clinical characteristics and outcome in 223 diabetic patients with deep foot infections. *Foot Ankle Int* **1997**; 18:716–21.
30. Eneroth M, Larsson J, Apelqvist J. Deep foot infections in patients with diabetes and foot ulcer: an entity with different characteristics, treatments, and prognosis. *J Diabetes Complications* **1999**; 13:254–63.