Linezolid in the Treatment of Osteomyelitis: Results of Compassionate Use Experience

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Abstract

Background: This case series examines osteomyelitis patients enrolled into a prospective, open label, non-comparative, non-randomized compassionate use program. Patients received 600 mg bid iv or po linezolid.

Patients and Methods: 89 patients were enrolled into the compassionate use program with the diagnosis of osteomyelitis and were evaluated for clinical efficacy, safety and tolerability. Informed consent was obtained from the patients or their guardians and guidelines for human experimentation of the US Department of Health and Human Services and/or those of the investigators' institutions were followed in the conduct of this clinical research.

Results: 55 cases of osteomyelitis met the inclusion criteria for clinical assessment. The 55 courses included long bone (53%), diabetic foot (18%), sternal wound (14.5%) and vertebral osteomyelitis (15%). Clinical assessment at long-term follow-up occurred at a median of 195 days after the last dose, and the clinical cure rate in 22 evaluable cases was 81.8% and failure rate 18.2%. The most common clinical adverse drug events (ADEs) were gastrointestinal disturbances. Reduction in hemoglobin/hematocrit and in platelet counts were the most common laboratory ADEs.

Conclusion: Linezolid iv or po was successful in treating patients with osteomyelitis caused by resistant gram-positive organisms or those with intolerance or non-responsiveness to other potentially effective treatments. Larger comparator controlled studies should be performed to confirm these findings.

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Introduction

Osteomyelitis is a common illness and its epidemiology is heterogeneous [1]. *Staphylococcus aureus* remains the primary pathogen in both community and nosocomially-acquired bone infections [2, 3]. The increasing prevalence of methicillin resistance [4] and the emergence of vancomycin resistance among strains of *S. aureus* are of major concern [4, 5, 6]. While community-acquired osteomyelitis is still primarily caused by methicillin-susceptible strains, a growing number of reports describing methicillin resistance among a variety of community-acquired infections are disturbing. Methicillin resistance among *S. aureus* (MRSA) and coagulase-negative staphylococci is frequent in nosocomially-related osteomyelitis, particularly in relation to osteomyelitis in the setting of orthopedic hardware-related infections [7].

Vancomycin-resistant *Enterococcus faecium* (VREF), a nosocomial isolate, is another gram-positive coccus that can produce bone infection [8–11] and, like methicillin-resistant staphylococci, is susceptible to only a limited number of antibiotics. Traditionally, the management of osteomyelitis caused by such resistant gram-positive pathogens requires the use of protracted courses of intravenous therapy with antibiotics such as vancomycin [12]. Patients allergic or intolerant to, or failing vancomycin, or unable to tolerate long-term intravenous therapy had been left with few to no therapeutic options. Thus, newer agents are needed for treatment of osteomyelitis due to resistant gram-positive cocci. Two agents now available with activity against these organisms include quinupristin/dalfopristin and linezolid. Linezolid, however, is the only agent approved for treating MRSA infections and has activity against both VREF and VRE faecalis [13, 14–16].

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The attractive features of linezolid, having 100% orally bioavailable dosage forms and adequate bone penetration [17, 18], prompted an analysis of outcomes among osteomyelitis cases enrolled in the linezolid compassionate use program. The linezolid compassionate use program provided a unique opportunity to examine the safety, tolerance and efficacy of linezolid when administered to patients with infections, including osteomyelitis, with other comorbid conditions or resistant organisms that precluded enrolment into other linezolid Phase III trials [19]. This manuscript is a more detailed description of the osteomyelitis cases than what has been previously published [19], focusing on clinical and safety outcomes of patients with osteomyelitis enrolled between October 1997 and May 2000.

Patients and Methods

This large case series examines osteomyelitis patients enrolled into a prospective, open label, non-comparative, non-randomized compassionate use program [19]. The purpose of the compassionate use program was to provide linezolid to patients infected with multidrug-resistant gram-positive organisms, who were intolerant to other potentially effective treatments, or to patients who could not tolerate long-term intravenous antibiotic therapy.

Patient Selection

Patients had to be at least 28 days old with signs and symptoms of a serious infection, such as fever, shaking chills and leukocytosis with a prominent shift to the left, or significant changes in vital signs. Patients were diagnosed with osteomyelitis by the treating physician with consideration of other relevant clinical, radiographic (e.g. computed tomography, radionuclide studies, magnetic resonance imaging), laboratory (e.g. erythrocyte sedimentation rate) and microbiological findings. Patients were expected to have had a clinical isolate of a gram-positive organism, preferably from a surgical sample that was considered to be the causative organism. Patients who were colonized (i.e. those with positive cultures without a documented infection) were excluded from the trial. The site investigators were required to complete the regulatory and sponsor-required documents, obtain local institutional review board approval and written informed consent and perform baseline evaluations, including medical history, physical examination, laboratory assays and blood cultures prior to the first dose of linezolid.

Dose and Duration of Therapy

Eligible patients received linezolid 600 mg intravenously or orally twice a day as monotherapy. There was no dosage adjustment required for patients with either renal or hepatic impairment. Duration of treatment was permitted for 5 days up to 3 months of therapy with prior approval. Site investigators whose patients required treatment for longer than 3 months were required to obtain an Investigational New Drug Application Status for the patient from the FDA after approval by the sponsor. Patients were allowed to be retreated at anytime if they met the original entry criteria and had not exceeded 3 months of therapy.

Baseline Assessment

If obtainable, confirmatory cultures from the site of infection and blood were repeated before the first dose of linezolid regardless of availability of local culture results. All baseline isolates were sent to a central laboratory (Covance, Indianapolis, IN, USA) for verification of identity, MIC determination and storage. Zone-of-inhibition susceptibility testing was performed at the local microbiology laboratory of the investigator before sending the organism to the central laboratory. Prior to the first dose of linezolid, the routine baseline laboratory tests included serum chemistry, hematology, liver function tests, urinalysis and pregnancy tests for females with childbearing potential. Life expectancy was assessed according to the modified McCabe Jackson scoring system [20].

Assessment of Clinical Outcomes

Assessments of clinical outcomes were performed at each site by the local investigators. Clinical cure was defined as a resolution of signs and symptoms of disease as noted at enrollment. Failure was defined as persistence of presenting signs and symptoms and/or new unfavorable findings subsequent to study entry. Clinical outcomes were designated as indeterminate if extenuating circumstances precluded classification to either a cure or failure, or where symptoms were in the process of resolving, but not totally resolved. Nonevaluable outcomes were ascribed when a patient was lost to follow-up (despite attempts at locating patient for follow-up assessment, patient could not be found, therefore follow-up assessment could not be performed) or if a patient had died (patient was dead by time of scheduled follow-up assessment, but the death was unrelated to infection; therefore it was not possible to perform a follow-up assessment).

Clinical outcome assessments were defined as short-term follow-up (STFU) and long-term follow-up (LTFU). The STFU was expected to occur 7–10 days after discontinuing the study drug if treatment was less than or equal to 28 days. If patients received more that 28 days of therapy, the STFU assessment was performed 1 month post treatment. The LTFU assessment was to be performed at a later time post treatment (preferably after 6 months to 1 year), and was not performed in some patients as a result of a protocol amendment not requiring LFTU at 6 months or one-year post therapy. At each assessment time, clinical efficacy was characterized as either cure, failure, nonevaluable or indeterminate. Patients were excluded from the assessment of clinical outcome if they received less than 5 days of therapy or if they did not have a confirmatory positive culture (preferably surgically obtained) within 7 days of starting linezolid or if they received concomitant effective antimicrobial therapy in the time prior to or following the initiation of linezolid.

Adverse Events and Tolerance

Safety laboratory evaluations included serum creatinine levels, liver function tests and hematology assessments. Each assessment was performed at the clinical site every 3 days for the first 21 days and at least weekly thereafter. Adverse drug events were assessed daily and their relationships to linezolid were intensively evaluated during daily telephone follow-up with each site. All treated patients (including patients who had negative cultures at baseline or received < 5 days of therapy) were evaluated for adverse events and the coordinating center clinicians assured that all serious medical events were reported promptly to the sponsor and the FDA. Adverse and serious medical events were characterized as definite (possibly or probably related to the reappearance of the reaction on rechallenge with study medication); probable (obvious causal relationship between adverse event and study medication and no other valid explanations, but no rechallenge); possible (existence of less robust causal relationship with study medication and the likelihood of alternative explanations); and not related (event not

related to study medication, usually attributed to diseases or other drugs).

Results

Patient Course Demographics

89 patients were enrolled into the compassionate use program with the diagnosis of osteomyelitis (determined by the investigator) and were evaluated for safety and tolerability. 55 cases of osteomyelitis met the inclusion criteria for clinical assessment, that is, they received at least 5 days of therapy, had a positive culture within 7 days of starting linezolid, and did not receive concomitant effective antimicrobial therapy prior to the initiation of linezolid or after commencement of linezolid therapy. 49 cases had positive cultures from surgically obtained specimens (including biopsies [84%] and aspirates). Surgical procedures performed included debridements, incision and drainage, removal of foreign material and amputation. In six cases the cultures were obtained from deep swabs and in these, colonization cannot be excluded, however, based on the clinician's judgement and supporting radiographic findings (X-ray and MRI) they were infected and required therapy. All cases of osteomyelitis met accepted clinical definitions for chronic osteomyelitis, since all cases had at least 14 days of symptoms as well as the presence of radiographic changes. In three of 55 cases where a concomitant bacteremia was noted, a biopsy had confirmed osteomyelitis.

The baseline characteristics among these 55 patient courses are summarized in table 1, which highlights the long durations of linezolid therapy, extensive use of the oral dosage form of linezolid, varying prior antibiotic exposures and patient co-morbidities. The 55 patient courses included long bone osteomyelitis (n = 29, 52.7%), diabetic foot osteomyelitis (n = 10, 18.2%), sternal wound osteomyelitis (n = 8, 14.5%) and vertebral osteomyelitis (n = 8, 14.5%). More than three-quarters of the causative organisms were MRSA (n = 25, 45.5%) and VREF (n = 17, 30.9%) as depicted in table 2. Nearly 30% of patients had foreign bodies (materials including pins, rods, screws, nuts) associated with their infections. Seven of these patients (12.7%) could not have the material removed. 40% and 60% of patients were expected to survive for 1 to 5 years and more than 5 years, respectively, as assessed using the modified McCabe Jackson scoring system [20].

Table 1
Baseline characteristics for osteomyelitis treatment courses (N = 55).

Characteristic	N (%)	Mean (range)
Age [years]	55 (100)	58 (30–81)
Male	26 (47.3)	
Duration of therapy ≤ 28 days	13 (23.6)	22.2 (15–28)
Duration of therapy > 28 days	42 (76.4)	52.3 (29–110)
Baseline MIC (µg/ml)	27 (49.1)	2.1 (1–4)
Baseline serum albumin (g/dl)	43 (78.2)	3 (1.6–4.9)
Location where treatment was started		
Intensive care unit	6 (10.9)	
General floor	40 (72.7)	
Outpatient	9 (16.4)	
Route of administration		
Intravenous only	9 (16.4)	
Intravenous switch to oral	19 (34.5)	
Oral only	27 (49.1)	
Long-term immunosuppression	3 (5.5)	
Diabetes	22 (40.0)	
Dialysis	7 (12.7)	
Foreign body (pins, rods, other surgical hardware)		
Without foreign body	39 (70.9)	
Foreign body (removed)	9 (16.4)	
Foreign body (not removed)	7 (12.7)	
Previous antibiotic therapy		
Vancomycin intolerance/allergy[a]	29 (52.7)	
Vancomycin failure	7 (12.7)	
Duration of vancomycin used immediately prior to linezolid (days)	17 (30.9)	24.8(4.0–84.0)
Quinupristin/dalfopristin intolerance/allergy[b]	9 (16.4)	
Quinupristin/dalfopristin failure	1 (1.8)	
Duration of quinupristin/dalfopristin used immediately prior to linezolid (days)	7 (12.7)	11.0(4.0–42.0)

[a] Previous intolerance or allergy to vancomycin included (adverse reaction [N]): rash ± fever (16); exfoliative dermatitis or Stevens-Johnson syndrome (4); leukopenia (1); eosinophilia (1); hives/swelling (1); ototoxicity (1); gastrointestinal complaints (1); loss of intravenous access (1); not specified (10). Some patients had > 1 intolerance/allergy documented; [b] Previous intolerance or allergy to quinupristin/dalfopristin included (adverse reaction [N]): arthralgia/myalgia (4); rash (2); nausea (1); exacerbation of congestive heart failure (1). Not specified (1). Some patients had > 1 intolerance/allergy documented

Clinical Outcomes

Clinical assessment at STFU occurred at a median of 21.0 days (mean 21.5 days, range 5 to 30 days) following

Table 2
Primary pathogens for the 55 osteomyelitis treatment courses.

Pathogen	N	(%)
Methicillin-resistant *Staphylococcus aureus*	25	(45.5)
Vancomycin-resistant *Enterococcus faecium*	17	(30.9)
Methicillin-susceptible *S. aureus*	3	(5.5)
Vancomycin-susceptible *Enterococcus* spp.	2	(3.6)
Methicillin-resistant *Staphylococcus epidermidis*	2	(3.6)
Vancomycin-resistant *Enterococcus faecalis*	2	(3.6)
Vancomycin-resistant *Enterococcus* spp.	1	(1.8)
Other	3	(5.5)

Table 3
Clinical outcomes among the 55 osteomyelitis treatment courses.

	N (%)[a]			
	Clinical outcome (STFU)[b]		Clinical outcome (LTFU)[c]	
ITT population				
Cure	38	(69.1)	18	(32.7)
Failure	7	(12.7)	4	(7.3)
Indeterminate	3	(5.5)	0	
Nonevaluable[d]	7	(12.7)	17	(30.9)
Not done[e]	0		16	(29.1)
Total	55	(100)	55	(100)
Evaluable population [a]				
Cure	38	(79.2)	18	(81.8)
Failure	7	(14.6)	4	(18.2)
Indeterminate	3	(6.2)	0	
Total	48	(100)	22	(100)

ITT: intention-to-treat; [a] (%) evaluable courses = (no. of cures, failures or indeterminates) ÷ (total number of courses – [non-evaluable + not done courses]) × 100; [b] STFU: short-term follow-up, occurred at a median of 21 days (range 5 to 30 days) following the last dose of linezolid; [c] LTFU: long-term follow-up, occurred at a median of 195 days (range 31 to 540 days) following the last dose of linezolid; [d] Nonevaluable: patient died from cause other than infection or patient lost to follow-up; [e] Protocol amendment meant 16 patient courses were not evaluated at LTFU

the end of treatment, and the clinical cure rate in evaluable cases was 79.2% and failures, 14.6%. 16 patient courses did not have LTFU performed due to a protocol amendment. Clinical assessment at LTFU occurred at a median of 195 days (mean 258 days, range 31 to 540 days) after the last dose of linezolid, and the clinical cure rate in evaluable cases was 81.8% and failure rate 18.2% (Table 4). 68% of LTFU assessments in evaluable cases occurred at least 6 months after cessation of linezolid. All clinical failures occurred at assessments made less than 5 months after cessation of linezolid. Clinical outcomes at SFTU were consistent with those at LTFU, with only one case designated a cure at STFU (30 days) that was a failure at LTFU (150 days or 5 months). Intent-to-treat analyses were also performed, but as expected, cure rates were considerably lower than those of the evaluable population due to the large numbers of non-evaluable cases (Table 3). There was no obvious tendency for one type of osteomyelitis to perform worse than another, however the number of evaluable cases becomes quite small as shown in table 4. The four clinical failures at LTFU were evenly distributed among the modes of administration; two failures were in patients who had an intravenous to oral therapy switch, and two failures were among patients receiving oral therapy only; however, the sicker patients received iv therapy. Only one of the four failures was associated with a foreign body: a washer in the cuboid bone of the left foot that could not be removed. Six of the seven clinical failures at STFU occurred with MRSA, where one of the seven failures occurred with VREF as shown in table 5.

Adverse Events and Tolerance

All 89 patients enrolled into the compassionate use program with the diagnosis of osteomyelitis were evaluated for safety and tolerability. There were 34 clinical adverse events identified by the primary investigator as possibly or probably related to linezolid. Of these, 16 courses were discontinued and five events were classified as serious. The most common clinical adverse events were gastrointestinal disturbances (nausea, vomiting and diarrhea) and cutaneous/dermatological reactions (rashes and itching) as illustrated in table 6. There were 31 laboratory adverse events considered possibly or

Table 4
Clinical outcomes by site of infection among evaluable osteomyelitis cases.

Site of infection	N (%)[a]					
	Clinical outcome (STFU)[b]			Clinical outcome (LTFU)[c]		
	Cure	Failure	Indeterminate	Cure	Failure	Indeterminate
Long bone osteomyelitis	24 (85.7)	3 (10.7)	1 (3.6)	13 (81.3)	3 (18.7)	0
Diabetic foot osteomyelitis	6 (66.7)	2 (22.2)	1 (11.1)	0	0	0
Sternal osteomyelitis	4 (80.0)	1 (20.0)	0	1 (100)	0	0
Vertebral osteomyelitis	4 (66.7)	1 (16.7)	1 (16.7)	4 (80.0)	1 (20.0)	0
OVERALL OUTCOMES	38 (79.2)	7 (14.6)	3 (6.2)	18 (81.8)	4 (18.2)	0

NE: non-evaluable; [a] (%) evaluable courses = (no. of cures, failures or indeterminates) ÷ (total number of courses – [non-evaluable + not done courses]) × 100; [b] STFU: short-term follow-up, occurred at a median of 21 days (range 5 to 30 days) following the last dose of linezolid; [c] LTFU: long-term follow-up, occurred at a median of 195 days (range 31 to 540 days) following the last dose of linezolid

Table 5
Clinical outcomes among the 55 osteomyelitis treatment courses by organism.

Organism	N (%)[a]					
	Clinical outcome (STFU)[b]			Clinical outcome (LTFU)[c]		
	Cure	Failure	Indeterminate	Cure	Failure	Indeterminate
MRSA	16 (69.6)	6 (26.1)	1 (4.3)	7 (63.6)	4 (36.4)	0
VREF	14 (93.3)	1 (6.7)	0	5 (100)	0	0
Other	8 (80.0)	0	2 (20.0)	6 (100)	0	0
Overall outcomes	38 (79.2)	7 (14.6)	3 (6.2)	18 (81.8)	4 (18.2)	0

MRSA: methicillin-resistant *Staphylococcus aureus*; VREF: vancomycin-resistant *Enterococcus faecium*; Other includes: methicillin-susceptible *S. aureus* (3); vancomycin-susceptible *Enterococcus* spp. (2); methicillin-resistant *Staphylococcus epidermidis* (2); vancomycin-resistant *Enterococcus faecalis* (2); other (4); [a] (%) evaluable courses = (no. of cures, failures or indeterminates) ÷ (total number of courses – non-evaluable courses) × 100; [b] STFU: short-term follow-up, occurred at a median of 21 days (range 5 to 30 days) following the last dose of linezolid; [c] LTFU: long-term follow-up, occurred at a median of 195 days (range 31 to 540 days) following the last dose of linezolid

probably related to linezolid, of which 20 resulted in discontinuation of therapy and 16 were considered serious (Table 7). Among the possibly or probably related cases with reduced hemoglobin or hematocrit (10), the average (range) baseline and nadir hemoglobin was 10.2 g/dl (7.8 to 12.6 g/dl) and 7.4 g/dl (6.2 to 8.2 g/dl) and the average (range) time to nadir was 35 days (9 to 60 days). Among the possibly or probably related cases with reduced platelets (9), the average (range) baseline and nadir platelet count was 226 $\times 10^3$/µl (133 to 342 $\times 10^3$/µl) and 62 $\times 10^3$/µl (21 to 141 $\times 10^3$/µl) and the average (range) time to nadir was 20 days (13 to 26 days). Among patients who had linezolid discontinued due to intolerance, there were three clinical failures and eight clinical cures.

Discussion

The analyses of compassionate use programs are often plagued by a large proportion of nonevaluable cases resulting from the severely debilitated patients who are recruited into such programs. The intention-to-treat analysis presented in table 4 emphasizes this limitation. Nevertheless, linezolid performed well overall among evaluable patients in this difficult-to-treat population. Clinical outcomes among 48 evaluable cases at STFU (median, 21 days) were consistent with those at LTFU, with only one case designated a cure at STFU (30 days) that was a failure at LTFU (150 days). Among the 22 evaluable patients at LTFU (median, 195 days), the cure rate was 81.8% and all patients with VREF and gram-positive infections other than MRSA were cured. More than 60% of the patients with MRSA-induced osteomyelitis were cured and although comparison data are difficult to find, the response to linezolid is probably not out of range of that seen with vancomycin treatment, especially recognizing that some patients had already failed protracted courses of vancomycin or quinapristin/dalfopristin and had unremoved foreign bodies. These cure rates are comparable to those seen in randomized trials of osteomyelitis in less complex patients [12]. In a current review of eight trials published to date, the cure (arrest) rate ranged from 50% to 100% [12].

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Table 6
Clinical adverse events considered possibly or probably related to linezolid by the investigator. (N = 89 patient courses with initial diagnosis of osteomyelitis).

Adverse event	N		
	All events	Events resulting in drug discontinuation	Events classified as serious
Gastrointestinal disturbances (nausea, vomiting, diarrhea)	18	7	0
Cutaneous/dermatological (rashes and itching)	9	5	0
Seizure	1	1	1
Anaphylaxis	1	1	1
Cardiac arrhythmia (supraventricular tachycardia)	1	1	1
Swollen/discomfort in tongue	2	0	0
Mucositis	1	0	1
Serum sickness	1	1	1

All patients were evaluated for adverse events provided they had received at least one dose of linezolid

Table 7
Laboratory adverse events considered possibly or probably related to linezolid by the investigator. (N = 89 patient courses with initial diagnosis of osteomyelitis).

Adverse event	N		
	All events	Events resulting in drug discontinuation	Events classified as serious
Decrease in hemoglobin/hematocrit	10	6[a]	5
Decreased platelet counts	9	7[a]	5
Elevated liver function tests/elevated bilirubin	1	1	1
Leukopenia	4	1	1
Increased serum creatinine	1	0	1[b]
Increased amylase/lipase (pancreatitis)	2	1	1
Reticulocyte count decrease	2	2	1
Increase in international normalized ratio (INR)	1	1	0
Red blood cell hypoplasia	1	1	1

All patients were evaluated for adverse events provided they had received at least one dose of linezolid. [a] Four patients had both decreased platelets and hemoglobin/hematocrit and in all these four cases linezolid was discontinued; [b] Patient had concomitant renal failure

dosage form was commonly recognized by the investigators treating these osteomyelitis cases: 84% of cases received oral linezolid at some time during their treatment and in 49% of patients it was the only mode of administration. Clinical failures were evenly distributed among the modes of administration: two (9.1%) failures were in patients who had an intravenous to oral therapy switch, and two (9.1%) were among patients receiving oral therapy only. However, patients receiving only oral therapy had more favorable baseline prognoses according to modified McCabe Jackson criteria. Based on these observations, it would be prudent to initiate linezolid therapy first intravenously and later switch to oral therapy, or possibly consider initiating oral linezolid therapy in patients with better expected outcomes or in those with functioning gastrointestinal tracts. Pharmacoeconomic results from the largest comparator-controlled study of MRSA infections illustrate that using an oral agent to treat MRSA instead of having to use intravenous vancomycin is an attractive and cost-effective option [21, 22]. It is also prudent to perform *in vitro* susceptibility testing of all isolates to insure that the infecting pathogens are sensitive to the antibiotic that is selected for use [23].

Linezolid has been observed to penetrate well into osteo-articular tissues in a case series of ten patients undergoing total knee replacement [17]. All but one linezolid concentration detected in synovial fluid (15.7–23.8 mg/l), synovial tissue (9.0–25.8 mg/kg), muscle (9.9–28.8 mg/kg) and bone (3.3–17.4 mg/kg) exceeded the minimum inhibitory concentration for 90% of staphylococci of 4 mg/l. In a more recent work [18], intraoperative tissue specimens from 12 patients who were undergoing hip replacement surgery were collected and linezolid concentrations were determined. The penetration into bone was rapid following a 20 min intravenous infusion of linezolid just prior to surgery. A mean concentration of 9.1 mg/l of drug was demonstrated in bone at 10 min after completion of the infusion. Mean bone concentration at 10 min following infusion was 51% of that achieved simultaneously in the blood. Linezolid penetration into fat and muscle tissue was also rapid and therapeutic concentrations (> 4 mg/l) of drug were maintained in the hematoma fluid surrounding the operative site for more than 16 h. In addition, recent case reports have documented favorable results with linezolid when used to treat prosthetic hip infections and vertebral osteomyelitis caused by VREF or MRSA [8, 11, 24].

The most extensive experience with long durations of linezolid treatment was in the compassionate use program [19]. 76% of patients received linezolid for more than the labelled maximum duration of therapy (28 days) with a mean of 52.3 days. This likely contributed to the number of reported adverse events. Duration-related adverse effects including reduction in platelets and hemoglobin would be expected to be maximal in these types of patients [25, 26]. Hematologic indices decrease slowly over time and can be detected with the appropriate monitoring of complete blood cell counts during treatment with linezolid and are reversible upon cessation of linezolid. Among the osteomyelitis patients who had linezolid discontinued due to intolerance (average duration of treatment 34.5 days, range 18–65 days), there were three clinical failures and eight clinical cures. In the intent-to-treat analyses, those eight patients who were clinical cures were not reclassified as failures because none of the patients required further antimicrobial therapy after the cessation of linezolid. It appears that even though the reason for stopping linezolid may have been due to intolerance in some patients, it had still been administered for durations sufficient for clinical cure in most cases.

In summary, patients with osteomyelitis due to resistant gram-positive cocci who were intolerant or failed to respond to vancomycin were generally successfully treated with linezolid. In addition, due to increasing cases of vancomycin resistance and linezolid having excellent tissue penetration and an oral formulation, it will be an important therapeutic option for treating these types of patients.

The results presented here should be interpreted within the context of the limitations in the study design. These include the non-comparative nature of the compassionate use program, the individual investigators diagnosing os-

teomyelitis, the large number of nonevaluable patients encountered, and the fact that many patients did not have LTFU assessments performed (even though STFU assessments were very consistent with LTFU assessments).

Future investigations should include randomized trials that compare the efficacy and safety of linezolid and comparators in patients with osteomyelitis caused by resistant gram-positive cocci.

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