Linezolid Treatment for Osteomyelitis Due to Vancomycin-Resistant Enterococcus faecium

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The incidence of nosocomial infections caused by vancomycin-resistant enterococci has risen substantially during the past 15 years. We report the use of linezolid for the successful treatment of hip prosthesis infection associated with osteomyelitis due to vancomycin-resistant Enterococcus faecium.

Strains of vancomycin-resistant Enterococcus faecium and, to a lesser extent, Enterococcus faecalis are becoming increasingly common nosocomial pathogens [1–3]. Infections caused by these organisms are difficult to treat because of the lack of consistently effective antimicrobial agents. Linezolid, a recently approved oxazolidinone antimicrobial agent, is active against many common gram-positive pathogens, including Enterococcus species [4, 5]. We report the use of linezolid for the successful treatment of hip prosthesis infection associated with osteomyelitis due to vancomycin-resistant E. faecium.

A 74-year-old white man who had osteoarthritis, for which he had undergone total arthroplasty of the left hip in 1982, presented with a 2-year history of gradually worsening left hip pain on weight bearing. In 1997, two years before presentation, he underwent hip revision surgery because he had been experiencing hip pain and difficulty with ambulation. The patient then fractured his proximal femur at the tip of the prosthesis. The fracture was repaired with a cable and plate fixation system that subsequently failed, and a second procedure was performed to stabilize the fracture. However, a nonunion fracture of the greater trochanter persisted, as did pain, and the patient was admitted to the hospital to undergo elective hip revision surgery. At presentation, he denied having experienced any associated fevers, chills, sweats, or weight loss. He reported no recent trauma and was physically active, biking for distances of >10 miles several times a week.

At examination, the patient was afebrile. His left leg was ~3 cm shorter than his right leg. He had decreased range of motion of the left hip and experienced pain on movement. The tissue surrounding the hip had thickened and was stiff, but no associated hip swelling, erythema, or warmth was noted. Preoperative cell counts and findings of serum chemistry analyses were within the ranges considered normal. Radiographs of the femur, hip, and pelvis revealed a loose prosthesis in the shaft of the femur, a long cable and plate fixation system along the side of the femur, heterotrophic bone around the femur and acetabulum, and a nonunion trochanter fracture. The reconstruction of the acetabulum was solidly fixed. The patient began receiving intravenous vancomycin and gentamicin perioperatively.

Operative findings included marked soft-tissue scarring and granulation tissue. The greater trochanter was loose, as were the associated cables and plate. Cloudy fluid and brownish granulation tissue consistent with a chronic infection were noted surrounding the plate. Frozen-section analysis as well as the final pathology report revealed synovitis with 2 microabscesses and scattered polymorphonuclear leukocytes (~20 cells per high-power field). As a result, the operative procedure was changed to radical debridement with removal of all metal implants. During removal of the cup, granulation tissue with an infected appearance was noted on the acetabulum, as were a significant bony defect in the acetabulum and lytic areas in the pubic and ischial rami. A large defect that involved the lateral shaft of the femur was noted after removal of the plate.

Administration of the antibiotics that had been given perioperatively was continued pending culture results. A second WBC count was 12,100 cells/µL, and the erythrocyte sedimentation rate (ESR) was 80 mm/h. The patient’s postoperative course was unremarkable, and he remained afebrile. Six days after surgery, 2 cultures of femur tissue yielded E. faecium. Susceptibility testing showed that the organism was resistant to ampicillin (MIC, >128 µg/mL) and vancomycin (MIC, >64 µg/mL) but was susceptible to linezolid (MIC, 1 µg/mL), chloramphenicol (MIC, =8 µg/mL), and tetracycline (MIC, =4 µg/mL). In addition, the organism was resistant to ampicillin-sulbactam, ciprofloxacin, erythromycin, levofloxacin, mero-

penem, penicillin, piperacillin, piperacillin-tazobactam, and tei-
coplanin. All MIC values were determined by agar dilution performed, according to National Committee for Clinical Lab-
oratory Standards, at Northwestern Memorial Hospital (Chicago, IL). No additional organisms were isolated from multiple aerobic and anaerobic tissue cultures. Two sets of blood cultures revealed no growth. No rectal colonization with vancomycin-resistant *E. faecium* was detected by culture. At this point, intravenous vancomycin and gentamicin therapy was discontinued, and treatment with oral linezolid was initiated.

The patient was treated with the recommended oral dosage of linezolid, 600 mg q12h for a total of 8 weeks. Plasma levels of linezolid, which were determined 1 h after (peak level) and just before (trough level) administration of an oral dose, were 13.7 and 3.0 µg/mL, respectively. Linezolid concentrations were measured by use of a validated, sensitive, and specific HPLC method (Pharmacia & Upjohn). During the course of treatment, the ESR gradually returned to a rate that was considered normal. The surgical incision healed without complication. Two weeks after therapy was begun, the patient developed an erythematous and scaly rash on the left posterior thigh, which was consistent with candidiasis. The rash resolved with topical use of clotrimazole. The patient tolerated the linezolid well and developed no hematological, hepatic, or renal abnormalities, as evaluated by weekly laboratory testing. During therapy, the lowest WBC count, hemoglobin level, and platelet count were 3600 cells/µL, 10.6 g/dL, and 245,000 platelets/µL, respectively.

Eight months after the patient completed therapy, laboratory studies revealed the following values: ESR, 6 mm/h; WBC count, 5700 cells/µL; hemoglobin, 14.4 g/dL; and platelet count, 272,000 cells/µL. Fourteen months after the completion of therapy, the patient had experienced no recurrent hip pain and was ambulating with the assistance of 2 canes. Because of extensive soft-tissue scarring and bony deformities, a new hip prosthesis has not been implanted.

To our knowledge, this is the first report of a patient with prosthetic joint infection and osteomyelitis due to vancomycin-resistant enterococci that were successfully treated with linezolid. Although no microbiological follow-up was possible, the patient clinically responded to treatment and remained free of pain for >1 year after the completion of therapy.

The oral bioavailability of linezolid is 100%, with peak levels near 18 µg/mL achieved 1–2 h after administration of an oral dose [5, 6]. This antimicrobial exhibits low protein binding and is eliminated via renal and nonrenal mechanisms [4, 5]. Organisms for which the MIC of linezolid is <4 µg/mL are considered susceptible, whereas those for which the MIC is ≥8 µg/mL are considered resistant [7].

The most common side effects associated with linezolid therapy are diarrhea, headache, and nausea [8, 9]. Increases in hepatic enzyme levels and thrombocytopenia have been reported. Thrombocytopenia is more likely to develop if the duration of therapy is >2 weeks. Additional cases of myelosuppression, including anemia, leukopenia, and pancytopenia, have been reported following prolonged therapy [8]. Therefore, it is recommended that hematological monitoring be performed weekly when therapy is prolonged.

In general, a bactericidal antimicrobial regimen is preferred for the treatment of osteomyelitis, because antimicrobial agents generally show poor penetration into bony tissue. Enterococcal osteomyelitis is generally treated with an aminoglycoside and either a β-lactam antibiotic or vancomycin, combinations that work synergistically to kill the enterococci; however, treatment remains difficult and relapses often occur [10]. Unfortunately, the emergence of multiple-drug resistance in enterococci poses a particular challenge for the treatment of osteomyelitis. Few cases of prosthetic joint infection or osteomyelitis due to vancomycin-resistant enterococci have been reported in the literature. One report described a diabetic patient who developed osteomyelitis due to vancomycin-resistant *E. faecium* in the cuboid bone of the foot following metatarsophalangeal joint resection [2]. Successful treatment involved administration of quinupristin/dalfopristin for 6 weeks, a revascularization procedure, and repeated bone debridements. Recently, 2 reports of prosthetic joint infection due to vancomycin-resistant enterococcal were published [11]. Control of these infections required extensive debridements along with administration of antibiotic therapy, which consisted of doxycycline in one case and chloramphenicol in the other. Neither patient received quinupristin/dalfopristin or linezolid therapy.

The patient in the present report had peak and trough levels of linezolid that were almost 14-fold and 3-fold greater, respectively, than the MIC of linezolid for the *E. faecium* isolate. Because adequate plasma levels of linezolid were achieved, and because the patient had undergone extensive debridement with removal of all hardware, it was decided that a prolonged course (8 weeks) of linezolid therapy was his best treatment option. No aminoglycoside or β-lactam was added to treatment, because linezolid has not been shown to exhibit synergy with these agents [4].

Given our experience, linezolid, in conjunction with adequate surgical debridement, may be useful for the treatment of osteomyelitis due to vancomycin-resistant enterococci when the MIC of linezolid for the organism allows for plasma drug levels that do not fall below the MIC. However, because the rate of relapse associated with enterococcal osteomyelitis is high, and because resistance can develop while patients are receiving prolonged therapy [12], careful long-term monitoring of such patients is required. To confirm adequate drug levels, it may be useful to obtain a trough level for linezolid (available from the Infectious Diseases Pharmacokinetic Laboratory at the National Jewish Medical and Research Center, Denver, CO; telephone, 303-398-1974).
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Pharmacia & Upjohn Co. (Kalamazoo, MI) supplied the linezolid via an expanded-access program and determined the plasma concentrations of linezolid. The institutional review board of Northwestern University approved this study.

References