Overuse of Zyvox Tied to Neuropathy

BY ALICIA AULT
Contributing Writer

WASHINGTON — Patients who develop neuropathy while taking the antibiotic Zyvox (linezolid) do so after prolonged overuse of the drug, a scientist with the Food and Drug Administration's division of anti-infective drugs reported at the Interscience Conference on Antimicrobial Agents and Chemotherapy.

Once the drug is discontinued, the neuropathy seems to resolve in only a minority of the affected patients, Olga Belen, M.D., said in presenting findings from a search of the FDA's adverse event report system from April 2000, when the drug was approved, to November 2003. Zyvox, an oxazolidinone, is made by Pfizer.

Dr. Belen found 55 reports of neuropathy: 41 cases of peripheral neuropathy, 4 of optic neuropathy, and 10 with both optic and other areas affected.

Fifty-two of the patients received 600 mg twice daily. The mean age was 51 years, with a range of 12-80 years. There were 24 male patients and 28 female, and 32 reports from the United States and 28 from overseas.

Neuropathies had not been observed in preclinical or clinical studies, but they began to appear in the postmarketing period. Pfizer added language to Zyvox's label in December 2002 saying that neuropathies had been reported, but usually in patients treated for longer than the recommended maximum treatment period of 28 days.

The recommended duration of Zyvox treatment for complicated and uncomplicated skin and skin structure infections and community-acquired pneumonia is 10-14 days. For the indication of vancomycin-resistant *Enterococcus faecium* infections, the recommended treatment is 600 mg intravenously or orally twice daily, for 14-28 days.

But the median duration of treatment for patients who had neuropathies was 127 days—well beyond the recommended treatment period. The majority of patients with neuropathies had been taking Zyvox for 90-180 days, Dr. Belen said at the conference, sponsored by the American Society for Microbiology.

Of the 55, nine patients recovered, nine had a partial recovery, and 15 had not recovered at the last reported follow-up. There were no outcomes reported for 22 patients.

Dr. Belen said she could not draw a conclusion that Zyvox was responsible for the neuropathies reported, since the adverse event report database is just a passive collector of information. The case series "provides a temporal association with neuropathy," she said.

When asked why there had been such long duration of use in the reports, Dr. Belen said it seemed that much of the use was for joint and lung infections, which may have prompted physicians to prescribe for longer periods. ■

Daptomycin vs. Resistant Blood Infections

BY DIANA MAHONEY
New England Bureau

BOSTON — Daptomycin may be an effective option for difficult-to-treat gram-positive bloodstream infections, John Segreti, M.D., reported at the annual meeting of the Infectious Diseases Society of America.

Daptomycin was effective for 18 of the 22 bacteremic patients without endocarditis and for 6 of the 9 patients with infective endocarditis.

In a retrospective study, 31 patients were treated with daptomycin (Cubicin) for bacteremia and/or infective endocarditis at two medical centers. Of these, 24 achieved clinical resolution of the life-threatening conditions, including all 11 with methicillin-resistant *Staphylococcus aureus* (MRSA) infection, 6 of 7 with methicillin-susceptible *Staphylococcus aureus* (MSSA) infection, and 5 of 11 with vancomycin-resistant enterococci (VRE).

These findings are particularly important in light of the increasing prevalence of serious infections involving gram-positive cocci and the increasing concern about antimicrobial resistance, especially in hospital intensive care units, said Dr. Segreti of Rush Medical College in Chicago. "Unfortunately, the gold standard for many serious gram-positive infections—vancomycin—is threatened. Its increased use for *S. aureus* infections leads to an increased risk for recurrent bacteremia and mortality.

"This may be a consequence of inadequate bactericidal activity of vancomycin, especially when treating some strains of *S. aureus*." Daptomycin is a more rapidly bactericidal agent than vancomycin, "which is critical when treating bloodstream infections, especially in eradicating the vegetative mass associated with infective endocarditis," he explained.

Between November 2003 and July 2004, 31 patients at Rush University Medical Center in Chicago and Fountain Valley (Calif.) Regional Hospital received 6 mg/kg daptomycin daily or every other day for bloodstream infections. Overall, 22 of the patients had been diagnosed with bacteremia only, 8 had culture-positive infective endocarditis, and 1 had culture-negative endocarditis.

In 24 cases, the patients had received prior antibiotic therapy for their infections, including vancomycin in 18 patients and linezolid in 4, but they required a change in treatment because of limited success of the initial therapy or because of intolerable adverse effects.

The pathogens identified in the study population included MRSA in 11 patients, VRE in 11, MSSA in 7, and coagulase-negative staphylococcus in 1; 1 other patient had an infection of unknown etiology. An analysis of the patient records showed that daptomycin was effective for 18 of the 22 bacteremic patients without endocarditis and for 6 of the 9 patients with infective endocarditis. The seven patients for whom treatment was not successful died during hospitalization.

In general, daptomycin was safe and well tolerated, even for extended durations of therapy, Dr. Segreti said.

Currently, daptomycin is approved for the treatment of complicated skin and skin structure infections. A clinical trial is underway to assess higher dosages of the drug as well as the optimal dosage and duration of treatment and the long-term efficacy for these infections, he said.

The results suggest that daptomycin "may provide an additional option for the treatment of bloodstream infections, not only for patients who fail prior antimicrobial therapy but also as initial therapy for patients at risk for drug-resistant gram-positive infections," he concluded.

Dr. Segreti and his colleagues in this investigation reported no financial interest in the manufacturer of daptomycin, Cubist Pharmaceuticals Inc. ■

Daptomycin Looks Like a Possible Option for Treating Difficult Bone and Joint Infections

BY DIANA MAHONEY
New England Bureau

BOSTON — Daptomycin may effectively treat gram-positive bone and joint infections and may be less likely than standard antimicrobials to cause drug resistance as a consequence of long-term therapy, Michael S. Finney, M.D., said at the annual meeting of the Infectious Diseases Society of America.

In a retrospective study, daptomycin (Cubicin) eradicated infections in 9 of 10 patients with gram-positive osteomyelitis, septic joint infection, septic arthritis infection, and/or bacteremia. The patients were treated at two medical centers between November 2003 and April 2004.

"Eight of the patients were infected with methicillin-resistant *Staphylococcus aureus* [MRSA], and enterococcus and streptococcus were isolated from two patients," said Dr. Finney of Fountain Valley (Calif.) Regional Hospital, where six of the patients were treated. The remaining four patients were treated at Rush University Medical Center in Chicago.

Daptomycin was effective in seven of the eight MRSA-infected patients and both of the non-MRSA patients. Of the 10 patients, 4 had osteomyelitis only and 6 had some combination of osteomyelitis, septic joint infection, septic arthritis infection, and/or bacteremia.

Nine had undergone prior unsuccessful treatment with one or more antibiotics: Eight received vancomycin, three received linezolid, and three received quinupristin/dalfopristin. Among the patients successfully treated with daptomycin were seven who had failed or could not tolerate vancomycin, which is often a first-line treatment for osteomyelitis.

The daptomycin treatment duration averaged 30 days, with a range from 21 to 42 days. "In general, the therapy was well tolerated, even for the longer treatment durations," he said.

Among the nine patients successfully treated with daptomycin were seven who had failed treatment with or could not tolerate vancomycin.

The one patient in the case series whose infection was not resolved had a relapse during daptomycin therapy, "possibly as a result of underdosing," he said. Because of renal insufficiency, the septic arthritis patient was started on alternate-day vs. daily dosing and was not adjusted to daily dosing once renal function improved. During treatment, the patient developed an epidural abscess from MRSA with reduced susceptibility to daptomycin.

Bone and joint infections are notoriously difficult to resolve, require prolonged treatment, and are associated with a high risk of recurrence. "Effective treatment requires the antibiotic to penetrate the site of infection at an adequate concentration to effectively kill the causative pathogen," Dr. Finney noted. Because gram-positive organisms, particularly *S. aureus*, are the predominant cause of these infections, the possibility of drug resistance further complicates treatment.

Vancomycin, a standard treatment for bone and joint infections, is not highly active against some gram-positive organisms, including *S. aureus*. In fact, he said, "studies have shown an increased risk of recurrence with vancomycin treatment for *S. aureus* osteomyelitis." Bacteriostatic antimicrobials such as vancomycin, which merely inhibit the growth of bacteria, may have a higher risk of causing drug resistance during therapy than do bactericidal agents such as daptomycin.

Daptomycin is approved for treating complicated skin and skin structure infections. The findings suggest that further studies are warranted to determine the agent's role in treating gram-positive bone and joint infections,and to determine optimal dosing, Dr. Finney said.

He and his colleagues in the study reported having no financial interest in the manufacturer of daptomycin, Cubist Pharmaceuticals Inc. ■