

Daptomycin Studied for Bone, Joint Infections

The drug's off-label use may be less likely to cause drug resistance due to long-term therapy.

BY DIANA MAHONEY
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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 medical record study, daptomycin (Cubicin) successfully eradicated infections in 9 of 10 patients diagnosed 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, Dr. Finney said.

"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 treating seven of eight MRSA-infected patients and both of the non-MRSA patients. Of the 10 patients, 4 had a diagnosis of 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, ranging from 21 to 42 days. "In general, the therapy was well tolerated, even for the longer treatment durations," Dr. Finney said. No patients had severe adverse effects; one stopped therapy at 3 weeks because of nausea, and another had a mild elevation in CPK levels but not enough to warrant discontinuing therapy.

The one patient in the case series whose infection was not resolved had a relapse during daptomycin therapy, "possibly as a result of underdosing," Dr. Finney 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 the course of therapy, 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 is a standard treatment for bone and joint infections, but it is not high-

ly active against some gram-positive organisms, including *S. aureus*. In fact, Dr. Finney said, "studies have shown an increased risk of recurrence with vancomycin treatment for *S. aureus* osteomyelitis." It is possible that bacteriostatic antimicrobials such as vancomycin, which merely inhibit the growth of bacteria, have a higher risk of causing drug resistance during therapy than do bactericidal agents such as daptomycin, he said.

Currently, daptomycin is approved for the treatment of complicated skin and skin structure infections. The findings from this case series suggest that further studies are warranted to determine the agent's role in treating gram-positive bone and joint infections as well as to determine optimal dosing, "to improve clinical outcomes and to reduce the risk of resistance," Dr. Finney said.

He and his colleagues in this investigation reported that they have no financial interest in the manufacturer of daptomycin, Cubist Pharmaceuticals Inc. ■

'Effective treatment requires the antibiotic to penetrate the site of infection at an adequate concentration to effectively kill the causative pathogen.'

Drug-Resistant Bloodstream Infections Respond to Daptomycin

BY DIANA MAHONEY
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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.

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 patients with methicillin-resistant *Staphylococcus aureus* (MRSA) infection, 6 of 7 patients with methicillin-susceptible *Staphylococcus aureus* (MSSA) infection, and 5 of 11 patients 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 because of limited success of the initial therapy or 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.

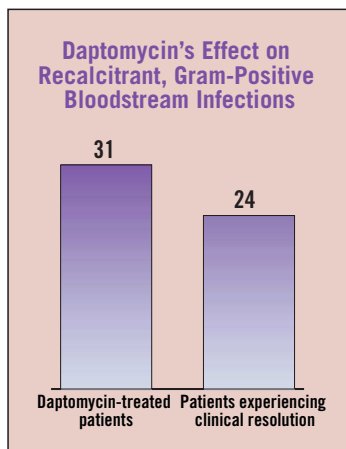
In general, daptomycin was safe and well tolerated, even for extended durations of therapy, Dr. Segreti said.

Currently, daptomycin is approved for the treatment of complicated skin and skin structure infections. A clinical trial is

underway to assess the efficacy of 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.

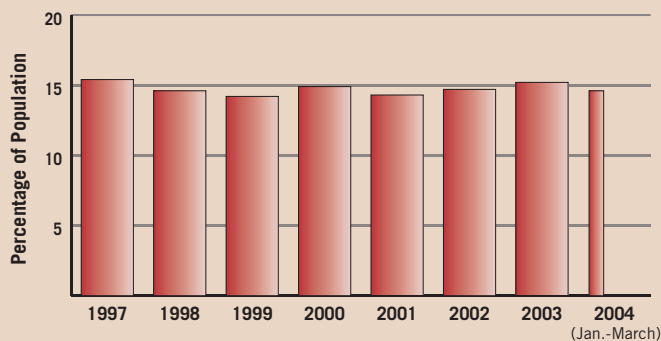
The results of this study suggest that daptomycin "may provide an additional option for the treatment of bloodstream infections, not only for patients who fail prior antimicrobial therapy but also as initial therapy for patients at risk for drug-resistant gram-positive infections," he concluded.

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



DATA WATCH

Lack of Health Insurance Coverage Holds Steady



Note: In early 2004, approximately 42 million people were uninsured in the United States. Source: Centers for Disease Control and Prevention