Antibiotics, DMARDs Have Role in Lyme Arthritis

BY DIANA MAHONEY
New England Bureau

BOSTON — Antibiotic therapy decreases the duration of persistent joint inflammation in Lyme arthritis, and disease-modifying antirheumatic drugs can reduce its severity in individuals with antibiotic-refractory disease, reported Dr. Alan Steere at a rheumatology conference sponsored by Harvard Medical School, Boston.

Antibiotics continue to be the cornerstone of treatment for Lyme arthritis, with the majority of patients responding to a 1-month course of oral doxycycline or amoxicillin, said Dr. Steere of Massachusetts General Hospital, Boston. In patients with mild, residual joint swelling, the oral antibiotic regimen is repeated for an additional 30 days. When joint swelling is moderate to severe, an additional month of intravenous antibiotic therapy with ceftriaxone, cefotaxime, or penicillin is a standard course, he said.

Management options have been less clear-cut, however, for patients with proliferative synovitis that persists for months or years despite antibiotic treatment, he said.

According to Infectious Diseases Society of America practice guidelines, patients with persistent postantibiotic joint swelling—whose joint fluid test results are negative for *Borrelia burgdorferi,* the spirochete implicated in Lyme arthritis—should be treated with nonsteroidal anti-inflammatory agents, intra-articular corticosteroid injections, or disease-modifying antirheumatic drugs (DMARDs). The guidelines also state that arthroscopic synovectomy should be considered for swelling that persists longer than 12 months (Clin. Infect. Dis. 2000;31:S1-14).

To evaluate postantibiotic treatment strategies in refractory patients and to compare treatment and disease course in antibiotic-responsive and -refractory patients, Dr. Steere and his colleagues reviewed the outcomes of 117 patients seen from November 1987 through May 2004. Of those, 50 were antibiotic responsive, and 67 had antibiotic-refractory Lyme arthritis.

All of the patients in the study met the Centers for Disease Control and Prevention criteria for Lyme arthritis as well as the Infectious Diseases Society of America guidelines for antibiotic treatment. The groups did not differ in age, sex, clinical presentation, duration of arthritis prior to diagnosis, or standard lab testing, according to Dr. Steere. Although the antibiotic-refractory patients tended to receive intra-articular steroids more often than the antibiotic-responsive patients did, "the majority of the refractory patients were not given this medication," he said.

One option in treating patients who have persistent postantibiotic joint swelling is to use disease-modifying antirheumatic drugs.

Comparisons between the responsive and refractory groups identified potential risk factors for antibiotic-refractory arthritis, including specific human histocompatibility leukocyte antigen-DR alleles, greater immune reactivity with the outer-surface protein A epitope, and treatment with intra-articular steroids prior to antibiotic therapy, Dr. Steere said.

In terms of treatment course, "in patients with antibiotic-responsive arthritis, a 1-month course of oral doxycycline was usually successful, while patients with refractory arthritis tended to have persistent disease even after 2 months of oral antibiotics and 1 month of IV ceftriaxone," Dr. Steere said, adding that type of therapy (oral antibiotics alone or combined with intravenous antibiotics) did not correlate with the postantibiotic duration of arthritis.

Patients in the refractory group underwent one of two different postantibiotic treatment strategies. Of the 67 patients, 22 were treated with NSAIDs or intra-articular corticosteroids. If their arthritis persisted for 12-24 months, they underwent arthroscopic synovectomy. In the remaining 45 patients, DMARD treatment (primarily hydroxychloroquine) was added to the previous regimen if polymerase chain reaction (PCR) testing was negative for *B. burgdorferi*. If the arthritis persisted, patients were given oral methotrexate for 3-4 months or two to four infusions of intravenous inifliximab, after which arthroscopic synovectomy was offered, if needed.

At follow-up, data for 20 of the 22 patients treated with NSAIDs or intraarticular corticosteroids showed that 11 patients had complete resolution of arthritis within a median of 11 months after the start of antibiotic therapy, whereas 9 patients underwent arthroscopic synovectomies. "Arthritis resolved in the all of the patients within a median of 14 months," Dr. Steere said.

Of the 42 patients treated with DMARDs for whom follow-up was available, 34 had resolution of arthritis within a median of 8 months after the start of antibiotic therapy. Three of the remaining eight patients who did not respond to treatment with hydroxychloroquine elected to have arthroscopic synovectomies, which was successful in only one patient, Dr. Steere said.

The two patients in whom the synovectomies failed, along with the remaining five with unresolved arthritis, received methotrexate or intravenous inifliximab, he said. Although both of the drugs induced responses, he said, "infliximab resulted in particularly marked reductions in joint inflammation."

Overall, arthritis persisted in the group of 42 patients who received DMARDs for a median of 9 months, Dr. Steere said. One patient in this group experienced a breakthrough case of persistent infection.

Based on these findings, a "reasonable management plan" for Lyme arthritis that persists after 60 days of antibiotics (including 30 days of intravenous therapy) should include an additional month of oral antibiotic therapy if PCR testing for *B. burgdorferi* DNA is still positive; treatment with NSAIDs if PCR results for *B. burgdorferi* DNA are negative; and the addition of 200 mg oral hydroxychloroquine twice daily if arthritis still persists, Dr. Steere said. If arthritis persists for 3-6 more months, arthroscopic synovectomy should be considered, he added.

Although DMARDs stronger than hydroxychloroquine were used in the investigation, "we're reluctant to recommend them, both because our limited experience with them doesn't prove efficacy and because of the possibility that they may be given to patients in whom the infection is still active," Dr. Steere noted.

Because Lyme arthritis eventually resolves even without antibiotic therapy, Dr. Steere and colleagues also sought to determine whether antibiotic treatment altered the natural course of the disease in patients with antibiotic-refractory arthritis.

To do this, they compared the current findings to those of 21 patients treated for Lyme arthritis in the late 1970s "before the etiologic agent of Lyme disease was known," Dr. Steere said. That group of patients received NSAIDs and intra-articular steroids, but not antibiotics, and experienced episodes of arthritis for a median period of 43 months.

In contrast, the median total time of arthritis episodes for the antibiotic-responsive patients and the antibiotic-refractory patients in the current study was 4 and 16 months, respectively. The finding suggests "antibiotic therapy decreases the period of joint inflammation, even in patients with antibiotic-refractory arthritis," he said. ■

Panel Backs Conditional Approval for Artificial Cervical Disk

BY ELIZABETH MECHCATIE
Senior Writer

GAITHERSBURG, MD. — A federal advisory panel supported the approval of a stainless steel artificial cervical disk for patients with single-level cervical degenerative disk disease, provided that the manufacturer evaluates long-term efficacy and safety in a post-marketing study.

The Food and Drug Administration's Orthopedic and Rehabilitation Devices panel agreed in a 7-0 vote that the Prestige cervical disk, manufactured by Medtronic, was "approvable" but recommended further study. The device is under review for use in skeletally mature patients with cervical degenerative disk disease (DDD) at one level from C3 to C7. DDD is defined as intractable radiculopathy and/or myelopathy that produces symptomatic nerve root or spinal cord compression because of a herniated disk or osteophyte formation.

Panelists agreed that the 2-year study demonstrated the safety and efficacy of the Prestige disk for this indication, but they were concerned about the long term because recipients of the device will have expected life spans of 30-50 years after implantation.

The two-piece device is made of stainless steel, with a metal-on-metal articulation and a ball and trough mechanism, which is affixed to the vertebral body with two bone screws. The device was compared with an anterior plated fusion procedure with structural allograft in a noninferiority, prospective, randomized study of 541 patients (mean age 43-44 years). The patients had single-level cervical DDD, inadequate response to 6 weeks of conservative therapy, signs of progression or spinal cord/nerve root compression, and a neck disability index (NDI) of 30 or greater.

Based on an interim analysis of the data at 24 months after surgery in 250 patients, 80.5% of the Prestige group and 71% of the fusion (control) group met the criteria for overall success (defined as at least a 15-point improvement in the NDI score, neurological maintenance or improvement, no serious adverse event that could be associated with the device, and no second surgery failure), according to Medtronic. Furthermore, the company said, radiographic evaluations indicated that patients' motion was maintained after surgery.

About 80% of patients in both groups experienced adverse events; most occurred perioperatively and resolved over time. The rate of device-related adverse events was 3% in Prestige recipients and nearly 10% in controls, a difference due mostly to cases of pending nonunions. Fewer nonunions and spinal events occurred in the Prestige group, while rates of urogenital adverse events were lower in the fusion group. There were three deaths among fusion patients and none in the Prestige patients.

Mean NDI scores improved by about 80% (15-point improvement) in both groups at 12 and 24 months.

Panelists recommended that the Prestige disk be described as "noninferior" rather than superior to the fusion procedure, because that was what the 2-year study had demonstrated. As another condition for approval, the panel recommended that the company conduct a study in animals to examine the generation and fate of particulate debris from the device, which is a concern associated with metal-on-metal devices.

Medtronic plans to evaluate the same end points, NDI, neurological status, second procedures, and adverse events in patients at 5 years and 7 years after surgery. In response to investigators' suggestions, the device's design has been modified and larger sizes have been added, but these were not studied in the trial, according to the company.

The FDA usually follows the advice of its advisory panels. If approved, the Prestige disk would be the first artifical cervical disk to be marketed in the United States. The agency previously approved two artifical lumbar disks. ■