EULAR Issues Fibromyalgia Treatment Guidelines

BY NANCY WALSH
New York Bureau

The fibromyalgia guidelines issued by EULAR represent a work in progress on a field "that is very much in evolution," Dr. Philip J. Mease said in an interview.

The recommendations were formulated by a European working group that included specialists from various fields including rheumatology, pain medicine, and neurology, who reviewed all the available trials through 2005.

"They have done a good job with a difficult challenge, because the trials are so different, both in terms of the outcome measures used and the treatment approaches tried," said Dr. Mease, a rheumatologist at the Univeristy of Washington, Seattle, and chief of clinical research at the Swedish Hospital Medical Center, Seattle.

"Moreover, they used a balanced way of looking at both pharmacologic and nonpharmacologic approaches, to give the managing physician a choice of therapeutic approaches," he said.

Among the general recommendations were the concepts that fibromyalgia requires a comprehensive assessment of pain, function, and psychosocial context. Treatment should be multidisciplinary, combining various modalities tailored to pain intensity, function, and associated features such as depression and fatigue. While recommendations were evidence-based where possible, these general recommendations regarding the heterogeneity of fibromyalgia and the need for multidisciplinary treatment were based on expert opinion.

Among the recommendations for nonpharmacologic measures were the use of heated pool treatment, with or without exercise. This modality was found to be effective in improving pain and function in several "fairly high-quality" trials, according to the investigators.

They reported that tailored exercise programs including aerobic exercise and strength training can be useful for some patients, and noted that the evidence in the literature for this recommendation is poor, with many open trials and inadequate blinding. However, given the safety and overall health benefits associated with exercise, they felt this should be included in the recommendations.

'Both pregabalin and pramipexole are recommended, but if you look at the specific trials they are vastly different.'

DR. MEASE

They also suggested cognitive-behavioral therapy may be beneficial for some patients. This recommendation was based on expert opinion, but the only two studies identified that evaluated this approach were of poor quality. However, "This is another area in which the poor quality of trials has masked what experts believe to be a realistic reflection of possible benefits," and cited potential improvements in pain and function (Ann. Rheum. Dis. July 20, 2007 [Epub doi:10.1136/ard.2007.071522]).

Other therapies such as relaxation, rehabilitation, physiotherapy, and psychological support also may be used, depending on individual needs. Some experimental evidence exists for the use of physiotherapy and connective tissue massage, but the recommendation for other such therapies, again, was based on expert opinion.

With regard to pharmacologic treatments, the working group recommended tramadol for the management of pain, based on two randomized controlled trials. They also favored the use of acetaminophen and other weak opioids.

However, they advised against the use of corticosteroids and strong opioids, because of their potential for significant long-term side effects and a scarcity of clinical trial data.

Antidepressants should be considered, the recommendations state, because of their ability to reduce pain and often to improve function. Amitriptyline, for example, was found to be beneficial in four of five trials that assessed pain according to a visual analogue scale (VAS).

The amitriptyline data exemplify a difficulty the investigators faced in their analysis when there were multiple trials evaluating the same drug, in that they averaged the effect sizes in these trials. With some trials being of high quality and others not, this may have skewed in an adverse way the effect size for amitriptyline, Dr. Mease observed.

Other antidepressants that have shown benefits in varying numbers and sizes of trials were fluoxetine, duloxetine, milnacipran, moclobemide, and pirlindole.

Another limitation acknowledged by the investigators was that for outcome measures they primarily relied on changes in pain assessed by VAS, and function as measured by the Fibromyalgia Impact Questionnaire (FIQ). They did not include the Short Form Health Survey (SF-36) or a patient global response, and today the outcome triad being used by the Food and Drug Administration to evaluate drugs for fibromyalgia includes a pain measure, some measure of function, and a patient global measure, said Dr. Mease, who chairs the international initiative on improving outcome measures in rheumatology known as OMERACT.

Finally, the investigators stated tropisetron, pramipexole, and pregabalin reduce pain and should be considered for the treatment of fibromyalgia. This recommendation illustrates a further difficulty faced by the EULAR group. "Both pregabalin and pramipexole are recommended, but if you look at the specific trials they are vastly different," Dr. Mease said. Pregabalin was evaluated in a multicenter, 500-plus patient trial that was very well controlled and excluded all other drugs that might influence fibromyalgia. In contrast, the pramipexole trial took place in a single center, with fewer patients and, importantly, permitted the use of background drugs including opioids, he said.

"This was a Herculean effort that was timely and appropriate, given the rising interest in fibromyalgia as a common condition that needs more attention," he said.

Another fibromyalgia expert, Dr. Robert M. Bennett of Oregon Health and Science University, Portland, offered a caution about pharmacotherapy in fibromyalgia. For instance, no mention is made of sleep medications or the adverse interactions of medications. "Tramadol has a dual action, as a weak opioid and a serotonin and norepinephrine reuptake inhibitor, and may interact with antidepressants, especially the monoamine oxidase inhibitors moclobemide and pirlindole, to induce a serotonin syndrome," Dr. Bennett explained in an interview.

The guidelines will be updated every 5 years, with the hope that good quality clinical trials will continue to add to the available evidence, wrote the investigators. ■

Singular Crystal Points the Way to a Pseudogout Diagnosis

BY DIANA MAHONEY
New England Bureau

BOSTON— To differentiate definitively between acute gout and pseudogout, look at the crystals.

On UV light microscopy, fluid aspirated from the inflamed joint of a patient with pseudogout will be teeming with rhomboid-shaped calcium pyrophosphate dihydrate (CPPD) crystals, which are morphologically different from the needle-shaped monosodium urate (MSU) crystals implicated in the pain and swelling of acute gout, Dr. Dwight R. Robinson said at a meeting on rheumatology sponsored by Harvard Medical School. "Calcium pyrophosphate dihydrate crystals are less well formed and show more variation in size and shape than monosodium urate crystals. In that way, they are a little more difficult to identify."

Like MSU crystals in the joints of gout patients, the deposition of CPPD crystals in pseudogout causes acute pain and swelling in one or multiple joints. The acute attacks can last anywhere from 1 day to 4 weeks and sometimes are accompanied by fever, leukocytosis, and elevated acute-phase reactants said Dr. Robinson, a rheumatologist and professor of medicine at Harvard Medical School, Boston. Because the latter signs also may be indicative of septic arthritis, sepsis first must be excluded by gram stain and culture of synovial fluid.

In general, CPPD crystals have a predilection for depositing in articular and fibrocartilage, said Dr. Robinson. In pseudogout, this process commonly involves the knee or wrist joint but also may involve the first metatarsophalangeal joint, as occurs in gout, or almost any other joint, he said. Radiographically, the diagnosis of pseudogout often can be confirmed by evidence of chondrocalcinosis in the affected joint space.

In addition to mimicking the clinical patterns of gout, the symptoms of CPPD joint disease may overlap with other inflammatory conditions. "The disease may present as pseudorheumatoid arthritis, pseudo-osteoarthritis with or without pseudogout, or pseudoneuropathic arthritis," said Dr. Robinson. "In many patients, the condition is actually asymptomatic."

CPPD disease develops idiopathically in individuals older than age 50. In younger patients, "it's more likely to be a complication of osteoarthritis, a late consequence of joint trauma or knee meniscectomy, or related to an underlying metabolic disease, such as hyperparathyroidism, dialysis-dependent renal failure, hemochromatosis, and hypomagnesemia," said Dr. Robinson, noting that there also may be a familial component.

Although the exact mechanism for the development of CPPD deposition disease is uncertain, an overactivity of enzymes that break down nucleoside triphosphates has been implicated, as have genetic defects, specifically mutations in the human homologue of the murine ANK gene. "Several mutations in the [human homologue] may be responsible for human disease, including CPPD arthropath," said Dr. Robinson.

There currently are no proven prophylactic therapies for pseudogout, but acute attacks can be treated effectively with, primarily, nonsteroidal anti-inflammatory drugs, said Dr. Robinson. Given the risks of gastrointestinal and renal toxicities associated with NSAIDs, particularly in elderly patients, intra-articular corticosteroid injection into the affected joint is a reasonable treatment option, he said, as is a short course of systemic corticosteroids for polyarticular pseudogout attacks. Oral or intravenous colchicine should be considered only as a treatment of last resort because of the associated risks of gastrointestinal and other toxicities. ■

©Dr. Gilbert Faure/Science Photo Library

Calcium phosphate crystals are seen in the knee of a patient with chondrocalcinosis.