Several Unusual Therapies Take Root in Europe

Many treatments may not reach the U.S. because small companies can't afford the FDA approval process.

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VIENNA — Americans attending the annual European Congress of Rheumatology are often impressed by the discussion of unfamiliar, even exotic therapies not available in the United States.

The most intriguing of these are supported by encouraging clinical trials data. Yet many of the therapies may never reach the U.S. market because they are the property of small companies that find the Food and Drug Administration approval process too fiscally daunting.

Here is a sample of novel therapies, currently unavailable in the United States, that were the subject of research presentations at the meeting, sponsored by the European League Against Rheumatism.

Diacerein

This plant-derived anthraquinone derivative blocks the downstream proinflammatory effects associated with stimulation of the interleukin-1 receptors located on chondrocytes and inflammatory cells. It doesn't affect prostaglandin synthesis.

EULAR guidelines categorize diacerein as a symptomatic slow-acting drug for both knee and hip osteoarthritis (OA). It is widely used for this purpose in much of Europe, where it has been the subject of more than a dozen randomized controlled trials.

At the EULAR meeting, Worowit Louthrenoo, M.D., presented the first randomized double-blind controlled trial of diacerein in an Asian population.

The Thai study involved 161 OA patients randomized to 50 mg b.i.d. of diacerein or 10 mg b.i.d. of piroxicam for 16 weeks, with an additional 8 weeks of follow-up post discontinuation, Dr. Louthrenoo said.

The primary end point in the TRB Chemedica–sponsored trial was pain relief as reflected in WOMAC scores.

At week 16 of the investigation, the diacerein group showed a mean 70% improvement in WOMAC scores, compared with baseline—not significantly different from the 74% improvement in the piroxicam group.

However, at week 20—which was 4 weeks following discontinuation—the mean improvement in the diacerein group remained at 67%, compared with 47% for piroxicam.

And at week 24, the diacerein group maintained a 70% improvement in WOMAC scores, versus a 27% improvement in the piroxicam group, said Dr. Louthrenoo, professor of medicine at Chiang Mai (Thailand) University.

The most frequent adverse event in the diacerein group was diarrhea; it was less common than the abdominal pain reported by piroxicam users.

Nuclear Magnetic Resonance Therapy for Low Back Pain

That's right—MRI not for imaging purposes, but as treatment. Therapeutic MRI, called MultiBioSignal Nuclear Resonance Therapy (MBST) was developed by a German company, Medtec Medizintechnik GmbH, after physicians serendipitously noted that patients with disabling chronic low back pain who had to undergo repeated conventional MRIs because of technical imaging problems reported feeling much better afterward.

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Physicians and physicists came up with a basic science rationale to explain the effect, then modified conventional MRI equipment to enhance it. They created a device that generates a static magnetic field and a three-dimensional alternating radiofrequency field designed to induce resonant vibration of hydrogen atoms within cartilage and bone in order to stimulate cell proliferation. Investigators at the University of Munich have previously demonstrated that MBST increases cartilage thickness in patients with knee osteoarthritis.

Sound flaky? Medical officials at one of Austria's largest workers' compensation insurer–funded inpatient rehabilitation centers don't think so, Werner C. Kullich, Ph.D., told this newspaper.

Dr. Kullich explained that the prevailing workers'-comp philosophy in German-speaking Europe is that rehabilitation of patients with chronic disabling low back pain is best accomplished through a 3- to 4-week inpatient stay at specialized centers that provide multimodal therapy, including extensive education, exercises, massage, hydrotherapy, and electrical stimulation. The results, though shown to be superior to the outpatient therapies that are the norm in much of the rest of the world, leave much to be desired—thus the insurance industry's interest in MBST and other novel approaches.

Dr. Kullich presented an insurer-sponsored, double-blind, placebo-controlled trial of MBST versus sham therapy in 62 rehab-clinic patients with chronic low back pain.

In addition to the standardized intensive 3-week inpatient rehab program, study participants received hour-long MBST or sham therapy sessions on 5 consecutive days. The study end points were changes in pain and function at 1 and 12 weeks post MBST.

Both groups showed significant improvements in low back pain as assessed by the Roland-Morris Questionnaire at 1 week; by 3 months, however, scores in the rehabilitation-plus-placebo group had returned to baseline levels, while the MBST group showed further significant improvement.

Similar results were seen on the Oswestry Disability Questionnaire. Particularly striking was the finding that after 3 months 74% of MBST-treated patients rated their ability to provide personal care as improved, and none indicated it had deteriorated, compared with baseline.

In contrast, only 37% of controls rated their personal care capability as improved, while 11% said it had deteriorated. Walking, sitting, standing, and lifting were areas where both groups showed significant improvement at 3 months, with greater gains recorded in the MBST group, said Dr. Kullich of the Ludwig Boltzmann Institute for Rehabilitation of Internal Diseases in Saalfelden, Austria.

Topical Diclofenac for Knee OA

A metaanalysis of four randomized controlled 4- to 12-week trials totaling 1,412 patients with symptomatic knee OA showed the topical agent's efficacy was equal to oral diclofenac and significantly better than placebo for the end points of stiffness, physical function, and pain on walking, according to Michael Doherty, M.D., professor of rheumatology at the University of Nottingham (England).

The number of patients needed to be treated with topical diclofenac for one patient to achieve greater than 50% pain reduction was six.

The chief advantage of topical as compared with oral diclofenac was that GI side effects were 43% less common with the topical agent and no more frequent than with placebo.

Topical diclofenac is contained in a dimethyl sulfoxide vehicle. The main adverse event associated with the topical therapy was local skin reactions, mainly dry skin and itching, which were 3.6-fold more frequent than with placebo.

The topical diclofenac solution, called Pennsaid, is approved for treatment of knee OA in Canada and seven European countries. A spokesman for Dimethaid Health Care Ltd., of Markham, Canada, told this newspaper the company hopes to gain U.S. marketing approval for Pennsaid in early 2007. The FDA has asked for two additional long-term safety studies, both of which are nearly completed.

Pentosan Polysulfate for OA

A non–commercially funded randomized double-blind placebo-controlled trial involving 114 patients with knee OA demonstrated that 4 weekly 3-mg/kg IM injections of pentosan polysulfate resulted in significantly greater improvements in pain at rest and walking, stiffness, and physical functioning involved in activities of daily living out to 24 weeks follow-up post treatment, reported Peter Ghosh, Ph.D., of the Institute of Bone and Joint Research at Royal North Shore Hospital, Sydney, Australia.

Pentosan polysulfate (approved in the United States only for interstitial cystitis) has been used in Europe for nearly 50 years as a postsurgery thromboprophylaxis agent. It promotes fibrinolysis and has anticoagulant activity. Dr. Ghosh saw its potential as a chondroprotective agent. "We have probably 50 papers of its effect in animals and in vitro. The rationale for its use in arthritis is solid as a rock," he told this newspaper.

"It mobilizes the clots in subchondral bone, it's anti-inflammatory, it protects the cartilage, and it stimulates the production in synovial fluid of hyaluronic acid. So it has all the markings of a disease-modifying drug for osteoarthritis," he said.

Pentosan polysulfate is marketed by bene-Arzneimittel GmbH of Munich. It's a small, family-owned company that does not have the financial resources to conduct a multiyear radiographic study with preservation of joint space as the end point, which is what the FDA insists upon if an OA drug is to obtain an indication as disease modifying.

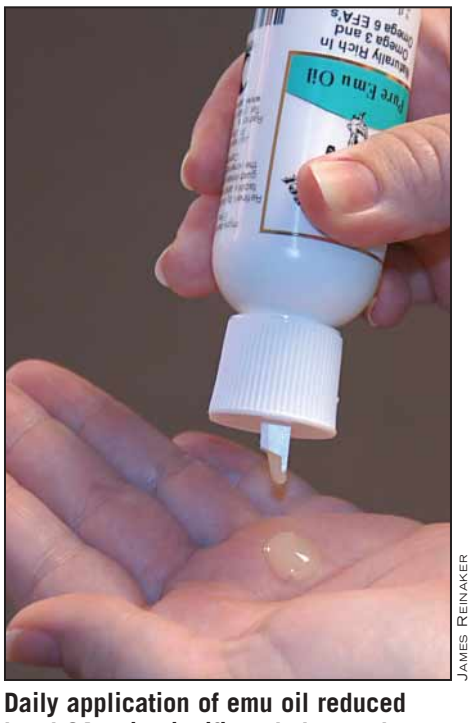
"They're looking for partners in Japan," he said.

In Europe, Canada, and Australia, pentosan polysulfate has become the leading drug for the prevention of progressive OA in dogs and horses. "In fact, we've been able to move much faster in the veterinary field than we have in humans," Dr. Ghosh added.

Emu Oil

Daily oral or topical use of oil rendered from the emu, a large flightless bird, resulted in a 2.34-fold greater reduction in pain than a canola oil placebo in a randomized double-blind trial involving 101 patients with OA hand pain. The observed treatment effect was medium to large, and it was apparent from week 4 onward in the 8-week trial, reported Melainie Cameron, Ph.D., of Victoria University, Melbourne, Australia.

As early as 1860, naturalists reported that Australian aborigines and early Anglo settlers used emu oil to treat wounds and relieve musculoskeletal pain, Dr. Cameron added. ■



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Daily application of emu oil reduced hand OA pain significantly better than canola oil or placebo.