Allopurinol Desensitization Effective in Select Patients

BY KERRI WACHTER
Senior Writer

DESTIN, FLA. — Oral desensitization appears to be a safe and effective alternative for patients who are allergic to allopurinol and who cannot take other urate-lowering drugs for gout, Adel G. Fam, M.D., reported at a rheumatology meeting sponsored by Virginia Commonwealth University.

While 1%-3% of patients experience a pruritic maculopapular rash in response to allopurinol, severe allopurinol hypersensitivity syndrome (AHS) occurs in only about 0.4% of patients, said Dr. Fam, a professor of rheumatology at the University of Toronto.

Dr. Fam suggested that allopurinol desensitization be considered in gout patients with any of the following circumstances:

► Renal impairment, which renders uricosuric drugs ineffective.

► Underexcretion hyperuricemia; and allergy, intolerance, or contraindications to both probenecid and sulfinpyrazone.

► Overproduction/overexcretion hyperuricemia, which coupled with uricosurics can increase the risk of renal stones.

► History of transplantation, renal insufficiency, and severe and debilitating gout.

► The patient requires prevention of malignancy-associated hyperuricemia and tumor lysis syndrome due to cytolytic therapy for hematologic malignancies; the resulting massive uricosuria precludes the use of uricosuric drugs.

The standard allopurinol desensitization protocol starts patients at a 50-mcg dose of allopurinol in suspension. The dose is gradually increased at 3-day intervals up to a target dose of 50-100 mg/day (in tablet form). The dosage can be adjusted if a rash occurs, Dr. Fam said at the meeting, also sponsored by the International Society for Clinical Densitometry.

For high-risk patients, a modified protocol is recommended. This protocol begins with allopurinol, 10 mcg or 25 mcg, in suspension. The dosage is titrated every 5-10 days.

In a retrospective study of 32 patients, 78% were able to tolerate long-term allopurinol therapy following desensitization (Arthritis Rheum. 2001;44:231-8).

The diagnostic criteria for AHS includes a definite history of exposure to allopurinol, lack of exposure to another drug that may have caused similar symptoms, and the fulfillment of either two major criteria or one major and one minor criterion. Major criteria include: worsening renal function, acute hepatocellular injury, and rash (toxic epidermal necrosis, erythema multiforme, diffuse maculopapular rash, or exfoliative dermatitis). Minor criteria include: fever, eosinophilia, and leukocytosis. ■

MRI Tool of Choice For Diagnosing RA, Expert Says

BY KERRI WACHTER
Senior Writer

DESTIN, FLA. — The advent of disease-modifying drugs has made magnetic resonance imaging an indispensable tool for diagnosing and monitoring patients with rheumatoid arthritis, Charles G. Peterfy, M.D., said at a rheumatology meeting sponsored by Virginia Commonwealth University.

MRI already is the tool of choice for use in clinical trials. Now it's time for clinical practice to incorporate this superior technology, said Dr. Peterfy, a radiologist specializing in musculoskeletal imaging, and chief medical officer of Synarc Inc., which specializes in radiology services for clinical trials. Radiographs have a number of shortcomings. Not only are they relatively insensitive for predicting disease progression and bone erosion, they are not accurate for measuring cartilage loss or for visualizing the synovium.

MRI can provide information on synovitis, tendonitis, and bone edema (or osteitis), all of which improve the predictive accuracy, particularly the negative predictive value. "The absence of these findings on MRI is a very powerful predictor that this patient is not going to progress," Dr. Peterfy said at the meeting, also sponsored by the International Society for Clinical Densitometry.

MRI of synovitis correlates with histopathology, Doppler ultrasound, PET imaging and "has been found to be more sensitive than clinical examination for swelling and tenderness," he said.

There are MRI techniques that allow the visualization of preerosive osteitis, which is key because osteitis can progress very rapidly, said Dr. Peterfy, who also is on the advisory board for MagneVu, the maker of portable MRI units. According to one study, baseline osteitis can predict functional disability at 6 years. A number of studies have demonstrated that MRI detects erosions earlier than x-rays, said Dr. Peterfy. In fact, one study demonstrated the ability of baseline MRI to predict bone erosions as much as 2 years later.

The development of a semiquantitative scoring system—such as the Rheumatoid Arthritis MRI Score (RAMRIS) developed by the European League Against Rheumatism–Outcome Measures in Rheumatoid Arthritis Clinical Trials (EULAR-OMERACT)—should help standardize the use of MRI to monitor the progression of RA. This system incorporates erosions, osteitis, and synovitis to assess disease changes. The group recently published an MRI atlas intended to improve the performance and generalizability of the MRI scoring system (Ann. Rheum. Dis. 2005;64 [suppl. 1]:i3-i55). ■

ALTERNATIVE MEDICINE
AN EVIDENCE-BASED APPROACH

Cat's Claw for Arthritis

History and Rationale for Use

In the medicinal system of the Ashaninka Indians of Peru, the human being is made up of body and spirit—flesh (*ivatsa*) and "deepest being" (*isancane*). As with many traditional systems, health is considered to be a state of harmony, with the literal translation of the phrase "I am healthy (*nocaratanaje*)" being "I carry harmony," according to Klaus Keplinger, who studied the Ashaninka during nine trips to the Amazon rain forest (J. Ethnopharmacol. 1999;64:23-34).

► *Peruvian Indians have long used preparations made from the cat's claw vine to treat various maladies.*

► *Two small clinical studies have suggested that the herb may have benefits in rheumatoid arthritis and osteoarthritis.*

According to the Ashaninka, disruptions in communication between body and spirit are a result of anxiety, and preparations of powerful plants (*saventaro*) that are inhabited by good spirits can eliminate these disruptions and restore health and harmony. One of these plants is *Uncaria tomentosa,* or uña de gato (cat's claw), so called because of its distinctive curling hooks. A decoction of sliced root bark boiled in water is used in traditional Peruvian medicine to treat numerous inflammatory disorders, ulcers, and infections.

Mechanisms of Action

Various hypotheses have been proposed to account for the purported clinical effects of cat's claw. One group of investigators has reported that the most likely mechanism for cat's claw's effects is immunomodulation via suppression of tumor necrosis factor–α (TNF-α) synthesis. The in vitro suppression ranges from 65% to 85% (Free Radic. Biol. Med. 2000;29:71-8).

Another group of researchers recently proposed that cat's claw's effects also derive from enhancement of DNA repair and immune cell responses through regulation of the nuclear transcription factor–β (NF-β), which controls nuclear events that protect the cell from apoptosis and also controls proinflammatory cytokine production (J. Ethnopharmacol. 2005;96:577-84).

In vitro studies also have identified free radical scavenging activity and inhibition of prostaglandin E_2 (PGE_2) production. The active principles thought to be responsible for these effects are pentacyclic oxindole alkaloids (POA). Two chemotypes of *U. tomentosa* exist; only the POA chemotype is immunomodulating (Planta Med. 1998;64:701-4).

Clinical Studies

A double-blind trial of an extract from *U. tomentosa* (Krallendorn capsules, made by Immodal Pharmaka GmbH, Volders, Austria) was recently conducted among a group of 40 patients with rheumatoid arthritis being treated at Innsbruck (Austria) University Hospital.

All patients had active disease and had been treated with sulfasalazine or hydroxychloroquine for at least 6 months; they were on stable doses of the drugs. Nonsteroidal anti-inflammatory drugs and daily doses of prednisolone up to 10 mg/day were permitted in the study.

Patients were randomized to receive one capsule (20 mg) of the plant extract or placebo three times per day for 24 weeks. During the next 24 weeks, all patients received the plant extract.

At the end of the first phase of the study, the number of painful joints had decreased by 53.2% in the active-extract group vs. 24.1% in the placebo group (J. Rheumatol. 2002;29:678-81). Statistically significant differences also were seen in the number of tender joints and duration of morning stiffness in the treatment group, but not in the placebo group, at 24 weeks compared to baseline.

No changes were seen in other parameters of efficacy, including patient assessment of disease activity, subjective assessment of pain, and laboratory markers, except for an increase in rheumatoid factor in the placebo group.

By the end of the second phase of the study, further significant improvements in the number of tender joints and duration of morning stiffness were seen among patients initially randomized to the extract group. Patients initially randomized to placebo also had significant improvements in the number of painful and swollen joints once they were switched to the active extract. They also reported decreased pain intensity, disease activity, and duration of morning stiffness, although these differences did not reach statistical significance. There was a nonsignificant decrease in rheumatoid factor in this group. One patient in the extract group withdrew because of gastritis, and one patient in the placebo group withdrew because of diarrhea. No serious side effects were reported.

Cat's claw has also been evaluated for use in knee osteoarthritis. In a multicenter double-blind study, 45 men were randomized to receive 100 mg of freeze-dried cat's claw or placebo daily for 4 weeks. The cat's claw group had significant improvements in pain associated with activity and in patient and physician assessment of disease activity. Improvements were seen as early as week 1 and continued throughout the trial (Inflamm. Res. 2001;50:442-8).

The authors observed a reduction in PGE_2 production, which they attributed to an inhibition of cyclooxygenase-2 expression. They wrote, "Of particular interest in the treatment of arthritis is the ability of cat's claw to not only confer benefit to the joints but also negate the side effects of NSAIDs on the stomach and intestine."

—Nancy Walsh