Gout Treatment Pipeline Includes Cherry Juice

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ROME – Last year's approval of febuxostat as the first new gout medication in over 40 years appears to have triggered a sharp uptick in drug development for a disease many physicians consider long neglected. The recent approval of pegoticase is proof of the pudding.

Novel gout therapies in the developmental pipeline range from the high tech – a fully human monoclonal antibody to interleukin-1beta – to the low tech, as in cherry juice.

"I've got more than 100 gout patients in my practice on cherry juice concentrate," Dr. Naomi Schlesinger said in an interview with RHEUMATOLOGY NEWS.

Her small retrospective study showed that consumption of 1 tablespoon of Brownwood Acres tart cherry juice concentrate twice daily – equivalent to eating 90-120 cherries – led to a 50% or greater reduction in acute gout attacks in 92% of treated patients, with no side effects. Prophylaxis with cherry juice concentrate is worth considering as an adjunct to urate-lowering therapy, said Dr. Schlesinger, chief of the division of rheumatology and connective tissue research at Robert Wood Johnson Medical School, New Brunswick, N.J.

As a result of its anti-inflammatory effect, cherry juice concentrate halves levels of interleukin-1-beta and TNF-alpha.

DR. SCHLESINGER

Many patients over the years had told her they loved to eat cherries and thought they might be helpful. Eventually she came across a small 1950 study suggesting a preventive effect.

"I've looked at pomegranate juice, too. It didn't work," she added.

The mechanism of benefit for cherry juice concentrate is an anti-inflammatory effect, the rheumatologist said. Her in vitro studies showed that cherry juice concentrate reduced by up to half interleukin-1-beta and tumor necrosis factor-alpha secretion by monocytes exposed to monosodium urate crystals.

In gout patients, cherry juice concentrate didn't lower serum urate levels; indeed, more than one-third of patients not on urate-lowering therapy who had averaged close to one attack per month remained attack free during 4-6 months on cherry juice concentrate despite an average serum urate level of 7.8 mg/dL.

Other novel gout therapies subjected to studies presented at the European congress included the anti-interleukin-1-beta monoclonal antibody canakinumab, a uricosuric drug known for now as RDEA594, and tranilast, which has been licensed in Japan for several decades as an oral mast cell inhibitor for treatment of asthma and allergic rhinitis.

Tranilast also has a potent serum uric acid–lowering effect, making it a potential therapy for chronic management of hyperuricemia in gout patients – one that already has a well-established track record for safety, according to Dr. Michael Kitt, executive vice president and chief medical officer at Nuon Therapeutics Inc., San Mateo, Calif.

He presented a preliminary study in which 49 healthy subjects who received 7 days of tranilast at 300, 600, or 900 mg daily showed dose-dependent 1.1- to 3.3-mg/dL reductions in serum uric acid. A phase-IIa study in hyperuricemic patients should be completed in time for presentation later this year at the American College of Rheumatology meeting, and a phase IIb study of tranilast plus allopurinol is just starting in gout patients. When commercialized, tranilast will be combined with allopurinol in a single tablet, Dr. Kitt said in an interview.

Dr. Schlesinger also presented a large phase II clinical trial in which canakinumab, the fully human anti-interleukin-1-beta monoclonal antibody, outperformed colchicine for the reduction of flares in gout patients starting allopurinol therapy.

The double-blind, multicenter, 24-week study included 432 gout patients starting allopurinol who were random-

ized to 16 weeks of colchicine at 0.5 mg/day, a single subcutaneous injection of canakinumab at 25, 50, 100, 200, or 300 mg, or monthly canakinumab injections at 50, 50, 25, and 25 mg.

The canakinumab regimens reduced the risk of one or more urate-lowering therapy-induced flares by 61%-80% compared with colchicine. Canakinumab also reduced the overall rate of flares by 48%-75% relative to colchicine.

Phase III studies are underway, and Novartis plans to file for marketing approval of canakinumab for the treatment and prevention of acute gout attacks by year's end. The monoclonal antibody is licensed as Ilaris for treatment of cryopyrin-associated periodic syndromes.

Dr. Fernando Perez-Ruiz presented a phase II study of RDEA594, a uricosuric drug that normalizes gout patients' underexcretion of uric acid by a novel mechanism: inhibition of reabsorption of uric acid in the proximal tubule of the kidney.

The study involved 123 hyperuricemic gout patients randomized to 4 weeks of RDEA594 at 200, 400, or 600 mg/day or placebo. All were on colchicine at 0.5-0.6 mg/day to reduce the rate of gout flares.

The primary end point – reduction of serum uric acid to less than 6 mg/dL after 4 weeks of treatment – was achieved in 45% of patients on the highest dose of RDEA594 and 0% of those on placebo. The median reduction in serum uric acid in patients on the highest dose was 38%, versus a 1% increase in the placebo arm.

Among the subset of patients with a baseline serum uric level below 10 mg/dL, as is the case for a large majority of gout patients seen in clinical practice, the response rate to the highest dose of RDEA594 was 58%. The side effect profile of RDEA594 was comparable to placebo, added Dr. Perez-Ruiz of Hospital de Cruces in Vizcaya, Spain.

Ardea Biosciences, San Diego, which is developing RDEA594, has not decided whether to take the drug into phase III trials as monotherapy or in combination with febuxostat, with which RDEA594 has shown synergistic effects, a company official said in an interview with RHEUMATOLOGY NEWS. ■

Disclosures: Dr. Schlesinger has received research grants from Brownwood Acres and Novartis. Dr. Kitt is employed by Nuon Therapeutics Inc. Dr. Perez-Ruiz is a consultant to Ardea Biosciences.