# Novel Agent Targets Osteoarthritic Knee Pain

BY BRUCE JANCIN
*Denver Bureau*

PARIS — Tanezumab, a novel inhibitor of nerve growth factor, significantly eased knee pain in patients with moderately severe osteoarthritis, according to the findings of a large, phase II, double-blind randomized trial.

Within 3 days after a first dose of tanezumab, many participants in the 440-patient trial experienced a greater-than-50% improvement in walking knee pain, as assessed by the Visual Analog Scale (VAS), Dr. Nancy E. Lane reported at the annual European Congress of Rheumatology.

"At higher doses, they had a 70%-80% reduction in knee pain that was maintained over 8 weeks. We've never seen that before, short of a joint replacement," she said in an interview. The trial was sponsored by Pfizer Inc., where Dr. Lane serves as a consultant.

Other possible applications for tanezumab include cancer pain, degenerative disk disease pain, and fibromyalgia, said Dr. Lane, professor of internal medicine and director of the center for healthy aging at the University of California, Davis.

Tanezumab is a humanized monoclonal antibody against nerve growth factor (NGF). NGF, which is upregulated in locally inflamed tissue and pain states, stimulates the growth of sensory nerve cells peripherally and increases the response to pain.

The subjects had moderately severe osteoarthritis knee pain, with average baseline walking knee pain VAS scores of slightly more than 70 mm on a 0- to 100-mm scale. All were unresponsive to nonopiate pain medications or were candidates for total joint replacement or other surgical interventions. After a washout period, they were randomized to intravenous placebo or tanezumab at 10, 25, 50, 100, or 200 mcg/kg. Two doses were administered 8 weeks apart.

Patients in the placebo arm averaged an 18-mm decrease in walking knee pain from baseline to week 16, as assessed by VAS. Those on 10-50 mcg/kg of tanezumab averaged 29- to 34-mm reductions. And those on 100 or 200 mcg/kg of the NGF inhibitor averaged 46- and 48-mm reductions, respectively, in VAS pain scores.

The most common adverse events related to tanezumab were transient episodes of hypoesthesia, which occurred in nearly 11% of patients at the two highest doses. These localized areas of numbness or reduced appreciation of pain are consistent with the inhibition of NGF, as NGF is a sensitizer to pain, Dr. Lane explained.

In the phase III trials to come, it's likely that weight-adjusted dosing will be replaced by three non–weight-dependent doses, perhaps 2.5 mg, 5 mg, and 10 mg. This dosing format allows for titration, which is attractive in treating chronic pain, the physician continued.

There is a pressing need for better pharmacologic therapies for osteoarthritis pain. Many patients can't tolerate, or don't obtain, adequate pain relief with NSAIDs. In addition, cardiovascular issues limit the usefulness of NSAIDs in many older patients. Narcotic analgesics are efficacious for the management of pain related to knee osteoarthritis and other chronic diseases, but these drugs entail problems with addiction and various toxicities. Inhibition of NGF may offer an effective alternative option.

"For patients with moderately severe osteoarthritis of the knee who [don't want] a joint replacement or who want to put it off, a treatment that lasts for 2 months gives them a 'pain holiday' to rest and restore their energy so they can better deal with their disease," Dr. Lane said. ■

# Fructose in Sugary Soft Drinks Is Implicated in Rise in Gout

BY NANCY WALSH
*New York Bureau*

LIVERPOOL, ENGLAND — Consumption of soft drinks containing fructose may underlie the sharp increase in gout in American adults that has occurred in recent decades, Dr. Hyon K. Choi said at the annual meeting of the British Society for Rheumatology.

Since 1967, when high-fructose corn syrup became commercially available and began to be used for sweetening soft drinks, there has been a 61% increase in the consumption of these beverages and a doubling of the incidence and prevalence of gout, particularly in men.

Conventional strategies for the prevention of gout have emphasized limiting consumption of purine-rich foods because uric acid is a breakdown product of purine. But fructose also can increase uric acid. The process involves the breakdown of adenosine triphosphate to adenosine monophosphate, a uric acid precursor, said Dr. Choi, a rheumatologist at the University of British Columbia, Vancouver.

Fructose also contributes to impaired glucose tolerance and increases insulin resistance and hyperinsulinemia, which could elevate serum uric acid levels.

Prospective studies have shown that sugary soft drinks contribute significantly to gout—as well as obesity, type 2 diabetes, and metabolic syndrome, he said.

In the large, ongoing health-professionals follow-up study of more than 51,000 men aged 40-75 years who answered dietary questionnaires and have been followed since 1986, a total of 755 new cases of gout have been diagnosed. The multivariate relative risk of gout for five to six servings of sugary soft drinks a week was 1.29; this rose to 1.85 for two or more servings a day, representing an 85% increase in incident gout in the highest consumers (BMJ 2008;336:309-12).

In another study that includes 14,761 participants aged 20 years and older from the third National Health and Nutrition Examination Survey (NHANES-III), serum uric-acid levels increased significantly with increasing sugary soft-drink consumption, with multivariate odds ratios for hyperuricemia being 1.82 in those who consumed four or more servings a day (Arthritis Rheum. 2008;59:109-16).

In both of these studies, the associations were independent of risk factors for gout including alcohol use, hypertension, and body mass index.

Data from NHANES-III, which is considered a nationally representative sample, also suggest that coffee may be protective, but only if it is drunk in large quantities, he said. After adjustment for age and sex, serum uric-acid levels in those drinking six cups of coffee a day were significantly lower by 0.43 mg/dL than in those who did not drink coffee (Arthritis Rheum. 2007;57:816-21).

The effect was not related to caffeine intake, as modest effects were seen with decaffeinated coffee, and none were seen in tea drinkers. "It could derive from other components in coffee such as chlorogenic acid or noncaffeine xanthines," he said.

In conclusion, patients at risk for gout should continue to emphasize limitations on purine-rich foods such as beer and certain meats. Purine-rich vegetables such as spinach and beans do not seem to elevate uric-acid levels, and need not be avoided.

Sugary soft drinks and other processed foods containing fructose should be avoided, not only for gout prevention but for prevention of the common comorbidities such as hypertension and obesity, he said.

Dr. Choi's work has been funded by the National Institutes of Health and the Arthritis Society of Canada. He said he has served on the advisory boards for TAP Pharmaceutical Products Inc. and Savient Pharmaceuticals Inc. ■

# *Allopurinol, Benzbromarone Are Equally Effective in High Doses*

BY JEFF EVANS
*Senior Writer*

Gout patients have equal rates of success in attaining a serum urate concentration of 0.30 mmol/L or less—a value thought to predict good control of flares and a reduction of tophi—with either allopurinol or benzbromarone, as long as the doses are slightly higher than normal and based on serum urate values, according to the results of a randomized, open-label trial. The data were presented at the annual meeting of the European League Against Rheumatism in Paris.

**'Allopurinol must be dosed higher than usually done in trials and in clinical practice to reach target serum levels.'**

**MR. REINDERS**

"Tolerability is not affected by doubling the dosage in patients not reaching target levels," said Mattheus Reinders, a hospital pharmacist at the Atrium Medisch Centrum, Heerlen, the Netherlands.

The results of the study make it clear that there is no difference in efficacy between allopurinol and benzbromarone, when given in adequate doses, despite their different mechanisms of action. It also shows "allopurinol must be dosed higher than usually done in trials and in clinical practice [300 mg/day] to reach target serum levels," Mr. Reinders said.

Gout flares and tophi mostly occur in those body parts with the lowest temperature: the extremities. It is often said that serum urate (uric acid) concentration—a well-accepted biomarker for evaluation of gout treatment—must be lower than the solubility at 37 °C (0.42 mmol/L) for good treatment. But solubility drops dramatically with lower temperature, and so lower serum urate values are needed. A serum urate concentration of 0.30 mmol/L or lower has been shown to be adequate in previous research, Mr. Reinders said in an interview.

EULAR's evidence-based recommendations for gout advise titrating the allopurinol dosage according to the level of serum urate that is attained. There is a lack of information about this approach and the effects of the higher dosages of serum urate–lowering drugs that will be required to decrease serum urate in patients who are not reaching target levels. Many clinicians also are prescribing only a fixed dosage of allopurinol 300 mg/day, he said.

Therefore, Mr. Reinders and his coinvestigators randomized 55 patients with newly diagnosed gout in an open-label trial comparing the efficacy and tolerability of allopurinol and benzbromarone. Allopurinol began at a dosage of 300 mg/day and was increased to 600 mg/day if necessary, while benzbromarone started at 100 mg/day and could be increased to 200 mg/day.

After 2 months of treatment, a significantly greater percentage of patients who took benzbromarone 100 mg/day reached the target serum urate concentration of 0.30 mmol/L (13 of 25 patients, or 52%) than did patients who took allopurinol 300 mg/day (8 of 30 patients, or 27%). After the investigators doubled the daily dosage of each drug in patients who had not met the treatment target, there was no significant difference in the total percentage of patients who had successful treatment with allopurinol (21 of 27, or 78%), compared with benzbromarone (18 of 23, or 78%).

Mr. Reinders conducted the research when he was in training at the Medisch Centrum Leeuwarden, also in the Netherlands, which funded the study. ■

Pages 40a—40b