IL-1 Blocker Shows Promise in Refractory Gout

Rilonacept resulted in a 75% improvement in pain scores in 5 of 10 patients after 6 weeks of injections.

BY BRUCE JANCIN
Denver Bureau

PARIS — The investigational long-acting interleukin-1 inhibitor rilonacept showed potential as an important new treatment option in patients with severe refractory chronic active gout in a small pilot study, according to a rheumatologist whose research focus is chronic gout.

Five of 10 patients in the single-blind nonrandomized study showed at least a 75% improvement in pain scores after 6 weekly subcutaneous injections of rilonacept at a fixed dose of 160 mg.

These were patients with severe refractory pain and disability at baseline, and none of them responded to 2 weeks of placebo injections, commented Dr. John S. Sundy, the director of rheumatology and allergy research at the Duke Clinical Research Institute, Duke University, Durham, N.C.

He disclosed that he is a consultant to Regeneron Pharmaceuticals Inc., which sponsored the pilot study.

Rilonacept is a soluble dimeric fusion protein and high-affinity blocker of the interleukin-1 receptor type 1 and the IL-1 accessory protein. Its therapeutic efficacy in this multicenter proof-of-concept study reinforces preclinical evidence and a small case series suggesting that IL-1 plays an important role in gouty inflammation, and that blockade of the IL-1 pathway represents a new treatment strategy in gouty arthritis.

The pathophysiologic sequence involves the engulfing of monosodium urate crystals by monocytes, which activates the cryopyrin inflammasome with resultant release of IL-1 into surrounding tissues.

The IL-1β induces expression of chemokines and adhesion molecules, which draw polymorphonuclear leukocytes to the site of acute inflammation, thereby making the inflamed joint even hotter, he explained.

The 10 participants in the pilot study had a mean age of 62 years, a 13-year history of gout, and a mean visual analog scale pain score of 5.1 at enrollment.

The patients had a mean of nearly three actively inflamed joints for at least the past month at enrollment.

Standard gout therapies were either ineffective or laden with unacceptable side effects in this overweight/obese population with numerous comorbid conditions.

High-sensitivity C-reactive protein levels (a measure of disease activity) dropped by an average of 59% after 6 weeks of rilonacept, then trended back up toward baseline during 6 weeks of follow-up off the drug. The number of affected joints decreased during active treatment, a trend that just missed statistical significance in this small study.

The same was true for physicians' global ratings.

Rilonacept was generally well tolerated. The most common reported side effect consisted of mild to moderate injection site reactions.

Speaking at the annual European Congress of Rheumatology, Dr. Sundy said that in addition to much larger and longer-term placebo-controlled trials of rilonacept in refractory chronic active gout, other trials are planned or underway to evaluate the IL-1 inhibitor for prevention of acute flares in patients with chronic gout, as well as in other inflammatory diseases in which the IL-1 pathway is believed to figure prominently.

These include juvenile idiopathic arthritis, familial Mediterranean fever, and rheumatoid arthritis.

Earlier this year, rilonacept received Food and Drug Administration marketing approval for the treatment of two rare cryopyrin-associated periodic syndromes: Muckle-Wells syndrome and familial cold autoinflammatory syndrome.

One audience member indicated that he wasn't bowled over by the 50% response rate reported by Dr. Sundy.

He questioned the merits of developing a sophisticated and costly new therapy for a familiar disease for which far simpler alternatives—including intra-articular corticosteroid injections—are often highly effective.

Dr. Sundy replied that rilonacept is targeted at the minority of patients in whom tried-and-true therapies aren't effective or are intolerable.

Given that gout is the most common inflammatory arthritis in men and its incidence is climbing, that's not an insignificant number of patients.

"This is the severe end of the spectrum of gout. It's the small tail on the curve, not the typical everyday presentation of gout," he stressed. ■

Allopurinol, Benzbromarone Both 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.

"In this small study, tolerability is not affected by doubling the dosage in patients not reaching target levels," study investigator Mattheus Reinders, a hospital pharmacist at the Atrium Medisch Centrum, Heerlen (the Netherlands), said in an interview.

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.

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

MR. REINDERS

A serum urate concentration of 0.30 mmol/L or lower has been shown to be adequate in previous research, Mr. Reinders said in the 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.

The gout diagnosis was confirmed by microscopic evidence of urate crystals in punctate from synovial fluid or periarticular structures or presence of tophi. The patients were indicated for serum urate–lowering treatment if they had tophi or more than two gout attacks per year. None of the patients had relevant liver or renal disease, and none had previously received either medication. Mr. Reinders conducted the research when he was in training at the Medisch Centrum Leeuwarden, also in the Netherlands, which funded the study.

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%).

Even before the dose increase, two patients stopped taking allopurinol and three stopped taking benzbromarone because of adverse drug reactions.

No more adverse reactions occurred after the dosages were increased in the nonresponders. ■

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