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 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 pathophysiological sequence involves the engulfing of monosodium urate crystals by monocytes, which activates the cryopyrin inflammatory complex 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 upward during baseline 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.

After 2 months of treatment, a significantly greater percentage of patients who took allopurinol 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 reached the target level, 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%).

More no adverse reactions occurred after the dosages were increased in the nonresponders.

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 usual to be used in trials and in clinical practice” (300 mg/day) to reach target serum levels,” Mr. Reinders said.

It was the first clinical study of allopurinol 300 mg/day, he said. “All patients must be dosed higher than usually done in trials and in clinical practice to reach target serum levels.”

Mr. REINDERS

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 those 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 did not reach 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.