Lesinurad Cuts Uric Acid in Refractory Gout

Ninety percent of patients who remained on treatment for 28 weeks met the study’s target level.

BY MITCHEL L. ZOLER
FROM THE ANNUAL EUROPEAN CONGRESS OF RHEUMATOLOGY
LONDON – An investigational drug that boosts uric acid secretion led to significant cuts in serum uric acid levels during 4 weeks of treatment in a phase II study of 208 patients with allopurinol-refractory gout.

In addition, among 30 patients who remained on the uricosuric agent lesinurad for 28 weeks in an extension phase, 27 patients (90%) reached the study’s target level of serum uric acid (lower than 6 mg/dL), according to Dr. Fernando Perez-Ruiz.

Data Source: A randomized, phase II study with 208 patients who were diagnosed with gout and whose serum uric acid levels remained above 6 mg/dL despite at least 6 weeks on steady treatment with 200-600 mg/day of allopurinol.

Disclosures: The study was funded by Ardea Biosciences, which is developing lesinurad. Dr. Perez-Ruiz said that he has had financial relationships with Ardea, Menarini, and Novartis. Dr. Dougados said he has been a consultant for and received research support from Roche.

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In a related study, the prevalence of metabolic syndrome was high in nearly 8,700 patients with hyperuricemia and gout, according to Dr. Fernando Perez-Ruiz.

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Major Finding: After 4 weeks of treatment with a combination of 200-600 mg/day lesinurad plus allopurinol and colchicine, 71%-87% of patients had serum uric acid levels lower than 6 mg/dL, compared with 28% of patients who were treated with allopurinol, colchicine, and placebo.

New Drugs Increase Excretion

“Until now, we have drugs that decrease uric acid synthesis, but we have not recently had any drugs to increase excretion,” Dr. Dougados observed, adding that “Now we have a new drug to increase excretion, and that is very important because allopurinol is often not sufficient to achieve the target serum uric acid level.”

Lesinurad works by inhibiting URAT1, a uric acid transporter molecule in the kidney that takes uric acid out of urine and places it back into the blood.

The study led by Dr. Perez-Ruiz enrolled patients who met the 1977 gout diagnostic criteria of the American Rheumatism Association (now the American College of Rheumatology) and who had a serum uric acid level greater than 6 mg/dL despite being on a stable dose of 200-600 mg allopurinol for at least 6 weeks.

Patients were randomized to daily treatment with 200 mg, 400 mg, or 600 mg of oral lesinurad or placebo.

All patients also received a 0.5-mg or 0.6-mg daily dose of colchicine, and all also remained on the dosage of allopurinol that they were taking at entry into the study.

After 4 weeks on treatment, the percentage of patients whose serum uric acid level had fallen below 6 mg/dL was 28% in the 72 placebo patients, and 71%, 76%, and 87% in the three lesinurad treatment groups, which each contained 42-48 patients.

The difference in the percentage of responding patients in each of the three treatment arms was statistically significant, compared with the placebo group.

“Lesinurad produced rapid and sustained reductions in uric acid levels when added on to allopurinol in patients who were not adequately responding to allopurinol alone,” Dr. Perez-Ruiz concluded.

To Reverse Metabolic Syndrome, Take Gout by the Horns

BY SHARON WORCESTER

Patients presenting with hyperuricemia or gout should be evaluated for metabolic syndrome, and any recommendations regarding dietary changes and medical treatment for gout should take into consideration the potential benefits of urate reduction, according to Dr. N. Lawrence Edwards.

Both hyperuricemia and gout are independent risk factors for metabolic syndrome and its individual components, said Dr. Edwards, professor of medicine at the University of Florida, Gainesville.

In a 2007 study looking at the prevalence of metabolic syndrome in nearly 8,700 patients with hyperuricemia from the NHANES (National Health and Nutrition Examination Survey) III database, the prevalence of metabolic syndrome increased in tandem with increasing levels of serum urate, and the increase persisted across subgroups stratified by age, sex, alcohol intake, body mass index, hypertension, and diabetes (Am. J. Med. 2007;120:442-7).

The investigators found that the prevalence of metabolic syndrome (defined using both original and revised National Cholesterol Education Program Adult Treatment Panel III criteria) was 19% in those with uric acid levels less than 6 mg/dL, 36% in those with 8.0-8.9 mg/dL, 62% for 9.0-9.9 mg/dL, and 71% for levels of 10 mg/dL or greater.

Physicians should recognize that metabolic syndrome occurs frequently in patients with hyperuricemia, and should be treated to prevent serious complications, they concluded.

In a related study, the prevalence of metabolic syndrome in patients with doctor-diagnosed gout from the same NHANES population was high (nearly 63%), compared with 23% in those without a gout diagnosis.

The prevalence was even higher (83%) among those with a more stringsly defined gout diagnosis (specifically those on urate-lowering therapy.). Dr. Edwards noted (Arthritis Rheum. 2007;57:109-15).

As with hyperuricemia, the investigators concluded that the prevalence of metabolic syndrome is high in individuals with gout, and that, given the serious complications that can be associated with metabolic syndrome, the condition should be recognized and taken into account when clinicians plan the long-term treatment of patients with gout.

The findings of these two studies support a pathogenic overlap between metabolic syndrome and gout, and underscore the importance of evaluating gout patients for the syndrome, Dr. Edwards said.

“You see a lot of patients coming in, and they haven’t had fasting glucose performed, blood pressures may be a little out of control, and weight is certainly out of control,” he noted.

“We need to look at these patients much more seriously than if they only have gout; they need a full-court treatment the potential benefits of urate reduction, according to Dr. N. Lawrence Edwards.

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“We need to look at these patients much more seriously than if they only have gout; they need a full-court press on all of their metabolic problems and not just their uric acid,” Dr. Edwards said.

Dietary recommendations that consist of the standard advice to avoid foods high in purines are not sufficient. Patients will often cut out meat and shellfish, but replace those with foods high in carbohydrates and fats, which can increase insulin resistance. Therefore, it is important to advise patients to reduce intake of high-purine foods, but also to avoid high-fat foods and the wrong kinds of carbohydrates.

About 40% of their diet should be complex carbohydrates, no more than 30% should be proteins, and no more than 30% should be mono- or polysaturated fats, he said.

As for medical treatment considerations, it is important to keep in mind the mechanisms of hyperuricemia as it relates to insulin resistance, he added.

In patients who are hypertriglyceridemic, for example, niacin is a commonly used drug.

However, niacin can elevate uric acid levels “by quite a margin” of 1.5-2.5 mg/dL. Conversely, fenofibrate can also be used to treat hypertriglyceridemia, and can lower the levels by a similar margin.

“So just making that switch might make a pretty substantial difference,” Dr. Edwards said.

In patients who are being treated for hypertension, keep in mind that hydrochlorothiazide is associated with elevated uric acid levels, and consider switching to the angiotensin receptor blocker losartan in those in whom hydrochlorothiazide is used solely for hypertension control and not for fluid control, as losartan has uric acid lowering effects, he said.

Dr. Edwards had no disclosures relevant to his presentation.