Allopurinol Failures Respond Well to Pegloticase

BY SHERRY BOSCHERT
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SAN FRANCISCO — The investigational drug pegloticase significantly reduced serum urate levels compared with placebo in two randomized, double-blind studies of 212 patients with gout who had previously failed treatment with allopurinol.

Patients received intravenous infusions of placebo or 8 mg pegloticase (Puricase) every 2 or 4 weeks in the 24-week Gout Outcome and Urate Therapy studies (GOUT1 and GOUT2), the results of which were presented by Dr. John S. Sundy at the annual meeting of the American College of Rheumatology.

Regimens of pegloticase every 2 weeks and pegloticase every 4 weeks rendered significant improvements in patients' serum urate levels.

At baseline, all patients had a serum urate level that was higher than 8 mg/dL (an average of 10 mg/dL) and severe, symptomatic gout, with three or more gout flares in the previous 18 months (an average of 10 flares), one or more tophi (present in 73% of patients), or chronic gouty arthropathy (present in 58% of patients in the studies).

The patient cohort had had gout for a mean of 15 years.

Allopurinol treatment was contraindicated or had failed to reduce serum urate to below 6 mg/dL in these patients.

Treatment in the study was considered successful if a patient's uric acid readings were within the normal range (less than 6 mg/dL) at least 80% of the time in months 3 and 6 of the studies.

None of the patients in the placebo groups of either the 104-patient GOUT1 study or the 108-patient GOUT2 study achieved this goal in the intent-to-treat analysis, according to Dr. Sundy.

However, on a regimen of pegloticase every 2 weeks, 47% of the patients in GOUT1 and 38% of patients in GOUT2 were treated successfully.

On a treatment regimen of pegloticase every 4 weeks, 20% of GOUT1 patients and 48% of GOUT2 patients achieved successful improvements, reported Dr. Sundy, who is a rheumatologist at Duke University, Durham, N.C., and his associates.

The serum urate improvements that were seen with both of the pegloticase regimens were significant compared with placebo, he commented.

Dr. Sundy disclosed that the company that makes pegloticase, Savient Pharmaceuticals, both funded the study and has given research funds or other payments to Dr. Sundy and many of the other investigators on this study, some of whom are Savient employees.

Additionally, Duke University and one of its employees who was not involved in the study hold patents on pegloticase.

A total of eight serious cardiovascular events occurred in patients getting pegloticase: two cardiac arrests, two exacerbations of heart failure leading to death in one patient, two dysrhythmias, one myocardial infection, and one case of angina.

Among other side effects, infusion reactions led to discontinuation of treatment in 11%-13% of patients on pegloticase and none on placebo.

Dr. Sundy said the cardiovascular events "may reflect underlying comorbidity."

A physician in the audience challenged this assumption, saying the events should occur in the placebo group, too, if that were the case.

A current, ongoing 12-month open-label extension of the study might soon shed some light on this, Dr. Sundy said.

Secondary measures of efficacy in the double-blinded studies found clinically and statistically significant improvements in the pegloticase groups compared with placebo.

Among patients with at least one tophus who were evaluated by computer-assisted photographic analysis, a tophus resolved completely in 21 (40%) of 52 patients getting pegloticase every 2 weeks and 11 (21%) of 52 patients getting pegloticase every 4 weeks, compared with 1 (4%) of 27 patients on placebo.

The number of tender joints decreased by seven in the 2-week pegloticase group and by six in the 4-week group compared with an average decrease of one tender joint on placebo. The number of swollen joints did not differ significantly between groups.

Both pegloticase groups, but not the placebo group, showed significant improvements in the Short Form–36 Health Survey physical component summary score and the physical functioning subscale of the Health Assessment Questionnaire–Disability Index.

The study cohort was 82% male, with a mean age of 55 years and a high degree of comorbidity.

Hypertension was present in 72% of patients, chronic kidney disease in 30%, diabetes in 22%, hypercholesterolemia in 21%, and coronary artery disease in 11% of the patients.

Pegloticase is a recombinant mammalian urate oxidase modified with polyethylene glycol that converts urate to allantoin. ■

Profoundly Lower Left Ventricular Mass Seen in RA Patients

BY BETSY BATES
Los Angeles Bureau

SAN FRANCISCO — Patients with rheumatoid arthritis have a "markedly" lower mean left ventricular mass than do age-matched controls, a finding that provides what may be a significant clue to elevated cardiovascular mortality in this population, according to a group of Maryland researchers.

The specific mechanisms underlying cardiovascular risk are only now being fully explored in this population, in part because RA patients often fail to present with the classic early signs and symptoms of cardiac disease, commented Dr. Jon Giles, who is a rheumatologist at the Johns Hopkins Division of Rheumatology in Baltimore, in a presentation given at the recent annual meeting of the American College of Rheumatology.

For example, Dr. Giles cited heart failure rates that are "nearly doubled" in RA patients.

Yet, "little is known about the myocardial changes that precede clinical heart failure in these patients," he said.

Dr. Giles and his associates turned to cardiac MRI, a highly sensitive tool for assessing left ventricular structure and function, to hunt for preclinical risk factors for heart failure.

Rheumatoid arthritis patients with moderate disease (average 7 years' duration) who enrolled in the ESCAPE RA trial (n = 75) were compared with 775 participants in the Multi-Ethnic Study of Atherosclerosis who did not have RA. None of the members of either group had a history of cardiovascular events or procedures.

The rheumatoid arthritis cohort was younger than was the control group (mean age 59, compared with 63), and was also less likely to have a diagnosis of diabetes (4% versus 14%) or hypertension (32% versus 49%).

However, the patients' mean unadjusted left ventricular mass was 18% lower (120 g/m^2 compared with 147 g/m^2), a difference that remained significant (at 14%) after subsequent adjustment for body surface area, age, gender, race, blood pressure, antihypertensive use, cholesterol and triglyceride levels, diabetes, and exercise.

The difference was particularly pronounced for male patients with RA, whose mean adjusted left ventricular mass was found to be fully 19% lower than that of men who did not have a rheumatoid arthritis diagnosis.

Female rheumatoid arthritis patients had a 9% lower left ventricular mass than did women without the inflammatory disease.

In both the RA and control groups, mean left ventricular mass decreased with age.

However, it was lower in rheumatoid arthritis patients than in controls in every age group, including the youngest patients in the study.

"In fact, the mean left ventricular mass was lower in 45-year-old RA patients than mean left ventricular mass in 80-year-old control patients, regardless of gender," Dr. Giles commented during his podium presentation.

Left ventricular stroke volume was marginally lower in RA patients than in controls, significantly so in men.

"Small but significant" reductions in adjusted mean ejection fraction were seen as well, Dr. Giles said.

No differences were seen in RA patients and controls with regard to adjusted mean end diastolic volume.

The Johns Hopkins team also explored potentially significant associations between cardiovascular risk markers and RA disease characteristics such as disease severity, activity, treatment, and systemic inflammation.

They found only two factors that were independently associated with left ventricular mass, stroke volume, and end diastolic volume in rheumatoid arthritis patients.

One factor was increased anti–cyclic citrullinated peptide antibodies.

The other was the use of biological disease-modifying drugs (predominantly tumor necrosis factor–α inhibitors).

No characteristics were associated with ejection fraction.

The study findings raise intriguing questions about whether rheumatoid arthritis and its treatment heighten patients' cardiovascular risk through different mechanisms than in the general, non-RA population, said Dr. Giles.

For example, markedly lower left ventricular mass may reflect the "aftereffects" of subclinical myocarditis.

On the other hand, lower left ventricular mass measurements "may support the concept that RA is a disorder of accelerated aging," he said.

Dr. Giles and his associates reported having no financial conflicts of interest with regard to this study. ■