

Febuxostat Found Safe in Renal-Impaired Patients

Results show that at a dose of 80 mg/day, serum urate levels fell below 6 mg/dL in 48% of patients.

BY TIMOTHY F. KIRN
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SAN DIEGO — Febuxostat was more effective than allopurinol for management of gout, even in patients with moderate renal impairment, according to data from a company-sponsored trial.

The 28-week trial, Febuxostat vs. Allopurinol and Placebo in Subjects With Hyperuricemia and Gout, known as APEX, revealed that 4 of 9 gout patients with moderate renal impairment (serum creatinine between 1.6 and 2 mg/dL) who received febuxostat at a dose of 80 mg/day achieved a serum urate level less than 6 mg/dL in their final three measurements, as did 5 of 11 patients who received 120 mg/day and 3 of 5 patients who received 240 mg/day.

None of the 10 patients with moderate renal impairment who received allopuri-

inol, at 100 mg a day, achieved that goal, Dr. H. Ralph Schumacher said at the annual meeting of the American College of Rheumatology.

Phase III results from the company-sponsored trial on febuxostat for gout were first reported at last year's annual meeting of the American College of Rheumatology. The presentation at the most recent ACR annual meeting included data on more patients as well as on those with renal impairment; the trial was shorter than the earlier investigation.

Dr. Schumacher's new report included data on 1,067 patients with gout and a serum urate level greater than 8 mg/dL followed for 28 weeks. Last year's report was on 760 patients, followed for 52 weeks.

The new results were very similar to last year's. Febuxostat at a dose of 80 mg a day decreased serum urate levels below 6 mg/dL in the last three measurements in

48% of patients. A dose of 120 mg a day reduced the last three measurements below 6 mg/dL in 65% of patients, and 240 mg a day reduced the last three measurements below 6 mg/dL in 69%.

The patients without renal impairment who received allopurinol received a dose of 300 mg a day, and, in those patients, the allopurinol reduced the last three measurements below 6 mg/dL in 20% of the group.

None of the patients on placebo had a reduction below 6 mg/dL in their last three measurements.

Dr. Schumacher noted that 90% of the patients on febuxostat had at least one serum urate measurement below 6 mg/dL during the trial. That compared with 40% of those on allopurinol and none on placebo. Of the subjects on 240 mg a day of febuxostat, 75% got at least one serum urate measurement below 4 mg/dL.

Tophi of the hands and feet decreased in size in patients on either active treatment, but the change was more significant among patients taking febuxostat, said Dr. Schumacher, professor of medicine at the

University of Pennsylvania, Philadelphia.

Types of adverse events were similar in the patients with and without moderate renal impairment; dose of febuxostat did not have an effect on adverse events, he added.

Gastrointestinal adverse events were most common and included diarrhea in 2%-4% of the patients on febuxostat and 7% of those on allopurinol.

Liver function abnormalities occurred in some patients and were deemed to be the result of colchicine use, used to manage gout flares and of little clinical concern, Dr. Schumacher said. Patients in all the groups had flares, particularly those on the highest dose of febuxostat, though the flares decreased over time.

Serum creatinine levels did increase slightly with febuxostat treatment. But those levels did not increase to any greater degree in the patients with moderate renal impairment than they did in those without renal impairment, he added. Dr. Schumacher received funding from the company that makes febuxostat, TAP Pharmaceutical Products Inc., Lake Forest, Ill. ■

Allopurinol Doesn't Work? Here's How to Lower Urate

BY BRUCE JANCIN
Denver Bureau

VIENNA — A wealth of hard-earned off-label tricks of the trade for serum urate lowering in gout patients who can't take allopurinol may soon fall by the wayside, forgotten in the rush to embrace an anticipated batch of new agents.

A variety of novel hypouricemic drugs intended to earn an indication for gout management are moving through the developmental pipeline. Furthest along is febuxostat, a nonpurine selective inhibitor of xanthine oxidase that has been submitted to the Food and Drug Administration for market approval. Also, looking good in phase II clinical trials for long-term urate lowering to prevent recurrent attacks of gout is a pegylated form of urate oxidase, Dr. Thomas Bardin noted at the annual European Congress of Rheumatology.

Allopurinol is the only readily available approved hypouricemic agent in most countries. It works well in most patients. But it is an old drug with many problems, and large numbers of patients either don't respond adequately, can't tolerate it, or have contraindications to its use. Until febuxostat and other hypouricemic drugs reach the marketplace, physicians who treat large numbers of gout patients will need to continue to reach deep into their bag of tricks in these situations, Dr. Bardin of Lariboisière Hospital, Paris, said at the congress, sponsored by the European League Against Rheumatism.

So what are the alternatives?

► **Lifestyle modification.** Avoidance of purine-rich dietary animal proteins and alcohol—especially beer—is a frequently neglected but effective means of lowering serum urate. So is weight loss.

► **Probenecid.** Having long taken a back seat to allopurinol because of its weaker urate-lowering effect, probenecid is being rediscovered by physicians. It should be started at 250 mg b.i.d., gradually increasing the dose every 2-3 weeks up to a target of 2 g/day.

► **Losartan.** Has a rapid effect, similar to probenecid. Urate lowering is not an ACE inhibitor class effect but is limited to losartan. The drug has the side benefit of reducing urine pH, thereby lessening the risk of uric acid stone formation. An excellent drug in gout patients with comorbid cardiovascular disease or hypertension.

► **Fenofibrate.** Doubles uric acid clearance. Another good choice in patients with cardiovascular disease or with hyperlipidemia. Dr. Bardin often uses it together with allopurinol in patients who don't reach the target serum uric acid level of less than 6 mg/dL with allopurinol alone. Other fibrates don't share fenofibrate's urate-lowering effect.

► **Switch antirejection drugs in transplant recipients.** Azathioprine, 6-mercaptopurine, and cyclosporine are often considered contraindications to allopurinol therapy because of harmful drug interactions. Dr. Bardin has persuaded transplant physicians to substitute mycophenolate mofetil with good results in gout patients he wants on allopurinol.

► **Desensitization therapy.** An option that can enable patients with cutaneous reactions to successfully go back on allopurinol. But it's a difficult, complicated, and bothersome procedure. "In the literature, you'll find a few cases of hypersensitivity syndrome occurring during desensitization. The patient needs to understand the risks, and that the drug should be stopped immediately in the event of skin rash," Dr. Bardin said. ■

View Asymptomatic Hyperuricemia As a Flag for Cardiovascular Risk

BY BRUCE JANCIN
Denver Bureau

VIENNA — The time has come for a change in thinking regarding nongouty asymptomatic hyperuricemia, traditionally dismissed as a clinically irrelevant laboratory abnormality, Dr. George Nuki asserted at the annual European Congress of Rheumatology.

"We actually need at this time a serious paradigm shift in thinking about the significance of asymptomatic hyperuricemia. We should think of it in terms of being a major prognostic marker. Asymptomatic hyperuricemia, as for gout itself, should be a red flag. When we see such a patient, we should ask ourselves why they're hyperuricemic, but we also need to assess them very well for cardiovascular risk factors and very carefully for metabolic syndrome," said Dr. Nuki, professor of medicine at the University of Edinburgh.

Serum uric acid can be measured simply and inexpensively. But the central question regarding its clinical significance in asymptomatic individuals remains unanswered: Is it an independent risk factor for cardiovascular and all-cause mortality, or merely a marker for other more causal risk factors?

The evidence remains conflicting. A Framingham Study analysis concluded that asymptomatic hyperuricemia was not an independent cardiovascular risk factor. But in several recent studies it was.

For example, in a prospective cohort study of 1,423 healthy middle-aged Finnish men followed for nearly 12 years, Dr. Leo K. Niskanen, professor of medicine at Kuopio (Finland) University, and coworkers found that men in the top one-third in terms of baseline

serum uric acid (SUA) levels were an age-adjusted 70% more likely to die of any cause than those in the lowest third. They were also 3.7-fold more likely to die of cardiovascular disease (*Arch. Intern. Med.* 2004;164:1546-51).

Similarly, in an analysis of data from the Losartan Intervention for Endpoint Reduction in Hypertension (LIFE) study, Dr. Aud Hoiggen, of Ullevål University Hospital, Oslo, and coinvestigators reported that baseline SUA was significantly associated with the cardiovascular event rate during 4.8 years of follow-up.

SUA rose over time both in hypertensive patients randomized to a losartan-based antihypertensive regimen and in those assigned to an atenolol-based regimen; however, the increase in the losartan group was 62% less. The investigators calculated that 29% of losartan's treatment effect on the primary LIFE composite end point of cardiovascular death, nonfatal MI, or stroke was attributable to the angiotensin-receptor blocker's effect upon SUA (*Kidney Int.* 2004;65:1041-9).

In addition, laboratory studies suggest that asymptomatic hyperuricemia might be an independent risk factor for cardiovascular disease.

Yet, despite growing evidence implicating nongouty asymptomatic hyperuricemia as a cardiovascular risk factor, Dr. Nuki argued there are insufficient data to warrant using allopurinol or other SUA-lowering drugs in affected individuals. Instead, he advocated lifestyle modification to reduce the hyperuricemia—less dietary intake of high-purine animal protein and alcohol, more exercise, weight reduction—coupled with aggressive pharmacotherapy of any metabolic syndrome present. ■