Febuxostat or Allopurinol for Gout? It Depends

BY MITCHEL L. ZOLER

Estimates of how many patients with gout should be treated with febuxostat range from just 5% to millions, according to experts interviewed for this article.

Febuxostat is clearly the second-line agent behind allopurinol, those same experts agreed. Allopurinol retains the top spot because of its substantially larger and longer track record and its dramatically lower cost.

Febuxostat received a warm welcome from gout specialists following its approval by the Food and Drug Administration 6 months ago. They cheered the arrival of the first new gout drug in decades, and early U.S. sales numbers for the drug were in line with expectations of Takeda Pharmaceuticals North America Inc., the company that markets febuxostat (Uloric), said Heather Dean, Takeda's marketing director for the drug.

Despite that, the type of gout patient who is a good candidate for febuxostat treatment remains controversial. At one end are some experts who say only a few gout patients—those who are truly intolerant of or unresponsive to maximum allopurinol treatment—are appropriate candidates. At the other end are specialists who say that febuxostat is the preferred drug for any gout patient who has moderate renal failure or who fails to respond to 300 mg/day of allopurinol, categories that encompass a sizeable number of symptomatic gout patients.

The decision to treat with allopurinol or febuxostat may be guided by some of the following considerations:

► Allopurinol (or more accurately, its active form in blood, oxypurinol) is excreted by the kidney, so patients with impaired renal function have higher blood levels of oxypurinol than do patients with normal kidneys. Allopurinol doses must be adjusted for these patients.

► Allopurinol is ineffective at the standard dosage of 300 mg/day for perhaps half of gout patients, but in most of these cases it's effective when the dose is raised; however, not all specialists are willing to prescribe the labeled maximum dosage of 800 mg/day.

► Febuxostat does not require any dosage adjustment in patients with renal impairment, and is labeled for use only at either 40 mg or 80 mg/day.

► Internet-based drugstores sell febuxostat at a cost of more than $5 a day, compared with an Internet cost as low as $0.10/day for allopurinol.

Patients With Renal Insufficiency

"About half the patients with chronic gout have significant impairment of renal function," said Dr. Peter A. Simkin, a rheumatologist at the University of Washington in Seattle.

But Dr. Simkin doesn't see impaired renal function as a barrier to allopurinol use. "It's both safe and appropriate to use allopurinol in patients with renal insufficiency," he said in an interview. "You start with a low dose and escalate slowly, but that's what we do with allopurinol for any patient." High blood levels of oxypurinol that can occur in patients with renal impairment must be avoided because they boost the risk of a hypersensitivity reaction, milder allergic reactions, or other forms of intolerance. Dr. Simkin said he had no disclosures relevant to febuxostat and allopurinol.

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Other specialists say that now that febuxostat is an option, they'll avoid potential problems by immediately jumping to the new drug for patients with impaired renal function. "Allopurinol should be first-line therapy in treating patients with hyperuricemia and gout unless their renal function prohibits use of allopurinol," said Dr. Robin K. Dore, a rheumatologist at the University of California, Los Angeles. Dr. Dore said she has been a consultant to and has been on the speakers bureau of Takeda, and she participated in some febuxostat studies.

But febuxostat should not be considered completely free from renal concerns, said Dr. Ted R. Mikuls, a rheumatologist at the University of Nebraska in Omaha. "Studies of febuxostat have not included patients with a serum creatinine level of more than 2 mg/dL that I'm aware of," he said in an interview. "The medical community must demand a lot more data before using [febuxostat] widely in patients with renal failure." Dr. Mikuls said he had no disclosures relevant to febuxostat and allopurinol.

"I am not convinced that careful allopurinol dose titration cannot achieve successful management of patients with impaired renal function," said Dr. Michael A. Becker, a rheumatologist at the University of Chicago. Dr. Becker said he has been a consultant to Takeda, and he was a coinvestigator on several of the febuxostat pivotal trials.

Allopurinol Intolerance

An estimated 5%-10% of gout patients are intolerant of allopurinol. Intolerance can range from a serious hypersensitivity reaction to a milder allergic reaction or another form of adverse event, such as gastrointestinal distress. A patient with hypersensitivity to allopurinol is someone for whom "febuxostat could be really helpful," but this is "pretty rare," Dr. Mikuls said. Problems such as stomach upset may occur in 5%-10% of patients, and this is another group of patients for whom "febuxostat can be really important," he added.

Lack of Efficacy With Allopurinol

For symptomatic gout, the guiding number rheumatologists look at is the serum level of uric acid. When the level drops below 6 mg/dL, existing uric acid crystals disappear by dissolving into the blood, thereby alleviating symptoms.

Although many patients respond to an allopurinol dosage of less than or up to 300 mg/day, most patients need more than 300 mg/day, Dr. Simkin said. "It's appropriate to use up to 800 mg/day," and although dosages of 300-800 mg/day are usually effective, doses this high are not often prescribed. "The main reason [why patients have uncontrolled gout] is misuse of allopurinol. Patients don't get treated with adequate doses."

Patients who don't respond to high allopurinol doses are "very rare," Dr. Simkin noted. He currently has "two such patients, and they're doing better on febuxostat," he said.

"A majority of the current gout patient population does not achieve a goal serum urate range of less than 6 mg/dL on 300 mg allopurinol," Dr. Becker agreed. However, "there is little evidence for allopurinol safety and efficacy [in dosages] greater than 300 mg/day," he said. Despite the lack of data, "I suspect that very few patients fail treatment with an allopurinol dosage of 600 mg or 800 mg/day," Dr. Becker said. Patients who do fail at these higher dosages are "probably not likely" to do any better on febuxostat, he added.

When patients don't respond adequately to 300 mg/day of allopurinol, Dr. Mikuls pushes the dosage as high as 800 mg/day, although he's not comfortable treating patients at this level. Patients who are still not at the serum uric acid goal at 800 mg/day should be switched to febuxostat, although it remains unclear how these patients respond following the switch. "I think we'd all like to see a data-driven answer to that question," he said.

"Every study of the quality of gout care suggests that patients get suboptimal care, including suboptimal use of urate-lowering treatments. If febuxostat serves any purpose, it's to highlight the condition and what is appropriate care," Dr. Mikuls said.

"In the rheumatology community, most of us routinely use [dosages of] allopurinol greater than 300 mg/day, but data collected by Takeda demonstrate that in the general medical community, 300 mg/day or less" is the dosage typically prescribed, Dr. Dore said. "Personally, I will increase the dose up to 400-500 mg of allopurinol per day before switching to febuxostat." ■

It May Be Time to Reconsider Allopurinol Dosing for Gout

BY AMY ROTHMAN SCHONFELD

PHILADELPHIA — A new study confirms what rheumatologists already know: Some patients with gout fail to achieve adequate reductions in serum urate levels with recommended levels of allopurinol.

For these patients, increasing the dose of allopurinol above the recommended dose can lower serum urate to target levels, according to Dr. Lisa Stamp, who presented her results at the annual meeting of the American College of Rheumatology.

"The problem with the guidelines is that many patients fail to achieve target serum urate levels of less than 6 mg/dL, the critical level above which gout is more likely to occur. We are … commonly undertreating" the disease, said Dr. Stamp, a rheumatologist at the University of Otago, Dunedin, New Zealand.

Dr. Stamp and her colleagues enrolled 90 patients with gout who were on stable doses of allopurinol for at least 1 month (mean age, 58 years; 88% male). After the initial visit, 52 were found to have serum uric acid levels greater than 6 mg/dL. Of those, seven received lower-than-recommended allopurinol doses, as defined by the Hande criteria based on creatinine clearance.

Allopurinol dosage was increased above the recommended range for 45 patients in 50- to 100-mg increments per month until they reached target serum uric acid levels. Of 36 patients who completed the entire 12-month study period, 85% (31 patients) achieved serum uric acid levels less than or equal to 6 mg/dL at 12 months. No serious allopurinol-related adverse events were reported.

All dose increases of allopurinol above recommended guidelines significantly reduced serum uric acid. The percentage decrease in serum uric acid from baseline was 12.6% when 50 mg was added to the recommended dose, 20.8% when 100 mg was added, 25.9% with 150 mg, 36.2% with 200 mg, 30% with 250 mg, and 35.6% with 300 mg. Some patients required dosage increases of up to 400 mg/day.

"My current recommendation is to first get the patient to the current recommended dose for at least 1 month before a dose increase. If that does not work, consider increasing the dose," Dr. Stamp said.

Notably, five of the patients who were initially found to have serum uric acid levels greater than 6 mg/dL were actually found to have no detectable plasma oxypurinol, indicating noncompliance. "You have to keep reminding patients the disease will come back if they stop taking the allopurinol," she added.

Dr. Stamp disclosed a relationship with Wyeth Pharmaceuticals. ■