

Febuxostat, Allopurinol Jockey for Role in Gout

Allopurinol remains the first-line agent in gout treatment, despite issues of kidney clearance.

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.

What is not debatable 6 months after febuxostat went on the U.S. market is that it's clearly the second-line agent behind allopurinol, the experts agreed. Allopurinol retains the top spot because of its substantially larger and longer track record and its dramatically lower cost.

Febuxostat (Uloric) received a warm welcome from gout specialists following its approval by the Food and Drug Administration. It was the first new gout drug in decades, and early U.S. sales numbers were in line with expectations of its marketer, Takeda Pharmaceuticals North America Inc., said Heather Dean, Takeda's marketing director for the drug. Several gout experts interviewed for this article said that they had no special concerns about febuxostat's safety, aside from the usual uncertainties that surround any drug when it first enters the market.

Despite that, the type of gout patient who is a good candidate for febuxostat treatment remains controversial. At one end are some experts who concede a scant few percent of gout patients—those who are truly intolerant of or unresponsive to maximum allopurinol treatment—as 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 fraction, perhaps even a majority, of symptomatic gout patients.

Some of the following facts that play into the decision to treat with allopurinol or febuxostat are undisputable:

► 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, a situation that demands dose adjustment.

► Allopurinol is ineffective at the standard dosage of 300 mg/day for perhaps half of gout patients, but in the vast majority of these cases it's effective when the dose is raised. Some specialists will prescribe the labeled maximum (800 mg/day) but many physicians are not comfortable prescribing such high doses.

► 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 drug stores sell febuxostat for more than \$5 a day vs. \$0.10/day for allopurinol.

But much of the split on how gout patients will do on allopurinol compared with febuxostat depends on opinion.

Patients With Renal Insufficiency

Impaired renal function is an issue in gout because uric acid crystals form in kidneys as well as in joints. Hyperuricemia itself may cause kidney damage. As a result, "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. Some experts, like Dr. Simkin, don'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. "The main thing [renal insufficiency] means is that patients can often be properly controlled with a low dose of allopurinol. Renal dysfunction is

not a reason to not use allopurinol. 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 reac-

tion, milder allergic reactions, or other forms of intolerance. Dr. Simkin said he had no disclosures relevant to febuxostat and allopurinol.

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.

The strategy of avoiding allopurinol entirely in patients with renal dysfunction and going straight to febuxostat was also endorsed by Dr. Naomi Schlesinger, a rheumatologist at the University of Medicine and Dentistry of New Jersey, in New Brunswick. Dr. Schlesinger said that she has served on an advisory board and the speakers bureau of Takeda, and that she has also received research funds from the company.

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 2.0 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." In addition, "I'm not aware of data that allopurinol damages kidneys. What most rheumatologists do is dose it very judiciously in patients with renal dysfunction, gradually increasing it to get the uric acid level where it needs to be." 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. But febuxostat may already be the "standard of care" for renal dysfunction patients, he said in an interview. Dr. Becker said he has been a consultant to Takeda, and he was a coinvestigator on several of the febuxostat pivotal trials.

Allopurinol Intolerance

A small percentage of gout patients (perhaps fewer than 10%) are intolerant of allopurinol. Intolerance can range from a serious hypersensitivity reaction to a milder allergic reaction or another form of adverse reaction, such as gastrointestinal distress. A patient with hypersensitivity to allopurinol is someone for whom "febuxostat could be really helpful," but this is "pretty rare, far less than a few percent," Dr. Mikuls said. "More common are other problems [with allopurinol], such as stomach upset. These reactions may occur in 5%-10% of patients, and this is another group of patients for whom 'febuxostat can be really important.'" Dr. Simkin differed slightly, estimating the total percentage of allopurinol-intolerant patients to be fewer than 5%.

Lack of Allopurinol Efficacy

In treating symptomatic gout, the guiding number rheumatologists look at is the serum level of uric acid. When the level drops below 6.0 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 (especially if they have renal dysfunction such that their blood level of oxypurinol is unusually high relative to their allopurinol dose), the majority of patients needs more than 300 mg/day, Dr. Simkin said. "It's appropriate to use up to 800 mg/day," and dosages of 300-800 mg/day are usually effective, he added. But doses this high are also not of-

ten prescribed by physicians. "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. There is no reason to think that febuxostat won't be effective in patients who had issues with allopurinol, he said.

'Millions' of U.S. gout patients, including those with renal problems, could benefit from febuxostat.

DR. SCHLESINGER

"It is clear that a majority of the current gout patient population does not achieve a goal serum urate range of less than 6.0 mg/dL on 300 mg allopurinol," said Dr. Becker.

"Many physicians do not like to go to a higher allopurinol dose." One reason is that "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. But some experts are cautious about any allopurinol dosage above 300 mg/day. No safety data exist for dosages over 300 mg/day of allopurinol, said Dr. Schlesinger. "Now that we have an option, these patients should probably be on febuxostat."

"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, said Dr. Dore. "Personally, I will increase the dose up to 400-500 mg of allopurinol per day before switching to febuxostat."

The Bottom Line

What does all this mean for the number of gout patients who should get febuxostat? On the low end, estimates range down to fewer than 5%, according to Dr. Simkin, whose total is mostly patients who are intolerant of allopurinol. On the high end, Dr. Schlesinger estimated that "millions" of U.S. gout patients need febuxostat, including all gout patients with chronic kidney disease, those who don't respond to a 300 mg/day allopurinol dosage, and those who are allopurinol intolerant. ■

