# Febuxostat Tied to Hypersensitivity Reactions

## *Reports include two cases of Stevens-Johnson syndrome.*

BY M. ALEXANDER OTTO

The Food and Drug Administration had received 11 reports of hypersensitivity reactions to febuxostat as of last month.

Among the 11 cases, there were 2 anaphylactic reactions, 1 case of angioedema, 2 of Stevens-Johnson syndrome, and 6 of rashes/allergies, the agency revealed in response to a request. Two patients were hospitalized; none died.

The information had not been made public until now.

At present, anaphylactic reactions and Stevens-Johnson syndrome are not mentioned in febuxostat (Uloric) labeling. Hypersensitivity is noted as a rare but possible adverse event.

The agency said in an e-mail that it is collecting febuxostat adverse event reports and will include them in a safety analysis to be completed in August.

The information is important because rheumatologists have been wondering how likely the drug is to cause hypersensitivity reactions, as it is typically used in patients who are intolerant of or allergic to allopurinol, which is associated with life-threatening, but rare, reactions.

The data do not answer that question, but do offer insight into it.

Takeda Pharmaceutical Co., febuxostat's maker, did not provide additional information when asked if the patients had kidney disease or allopurinol hypersensitivity. "We have been and will continue to work closely with the FDA to capture and monitor adverse events, as is our standard practice," a Takeda spokesperson wrote in an e-mail.

Dr. Brian Mandell, a Cleveland Clinic rheumatologist, said that he is not surprised by the reports.

"Someone, somewhere is going to react to every drug . [There's] no free lunch," Dr. Mandell said in an interview.

But, he added, "it is imperative that physicians realize that febuxostat can cause such reactions. There has been a tacit assumption that because it [has] a different molecular structure than allopurinol, such reactions will not occur."

**Rheumatologists have been wondering how likely the drug is to cause hypersensitivity reactions, as it is typically used in patients who are intolerant of or allergic to allopurinol.**

Febuxostat was approved by the agency in February 2009 for long-term management of chronic hyperuricemia in gout patients.

There were 139,565 prescriptions written for it in the United States in 2009, according to SDI Health LLC, a health care market insight and analytics firm.

No hypersensitivity reactions were attributed to febuxostat in trials comparing it to allopurinol, but allopurinol-sensitive patients were excluded, according to a briefing document that Takeda submitted to the FDA's Arthritis Advisory Committee in 2008 as well as the meeting transcript.

In trials, 1.6% of patients developed rashes in both the 80-mg febuxostat group and the allopurinol group, most of whom were on 300 mg. Among those in the placebo group, 0.7% developed rashes, according to febuxostat's label.

In early May, at a rheumatology conference sponsored by the University of California, Los Angeles, Dr. Mandell said, "the idea [that] you can give [febuxostat] to patients who are allopurinol hypersensitive is a guess. We just don't know."

Allopurinol hypersensitivity syndrome, although rare, is a significant concern for physicians who use the drug to lower serum uric acid in patients with gout. Symptoms can include liver and kidney damage, Stevens-Johnson syndrome, and toxic epidermal necrolysis. It is fatal about 30% of the time. The majority of cases occur in patients who have chronic kidney disease.

While the medical community awaits additional febuxostat postmarketing safety data, Dr. Mandell said that he uses febuxostat in allopurinol-intolerant patients, but told attendees he doesn't think it's more effective.

He said that he doses febuxostat just as carefully as he doses allopurinol. As with allopurinol, he starts patients on a low dose and titrates up slowly, monitoring for tolerability and also to ensure that uric acid levels aren't dropped too precipitously, which can trigger gout attacks.

With both drugs, Dr. Mandell said that he tells patients to stop taking them if they develop a rash or any other hypersensitivity reaction symptoms, and to call him.

The treatment goal is to reduce the serum uric acid level to 6 mg/dL, with ongoing labs to ensure that it's reached.

He hasn't had a hypersensitivity reaction with febuxostat, "but my 'n' is 9," he said in his presentation.

Although the lowest-dose febuxostat pill is 40 mg, he starts patients at 20 mg.

"Though the company suggests not to, I cut the pill," he said. ■

***Disclosures:*** *Dr. Mandell disclosed that he is an advisor to Takeda and URL Pharma Inc., and he was a clinical investigator for Savient Pharmaceuticals Inc.*

# Resistance Exercise May Preserve Muscle Mass in Arthritis

BY M. ALEXANDER OTTO

EXPERT ANALYSIS FROM A RHEUMATOLOGY SEMINAR SPONSORED BY UCLA

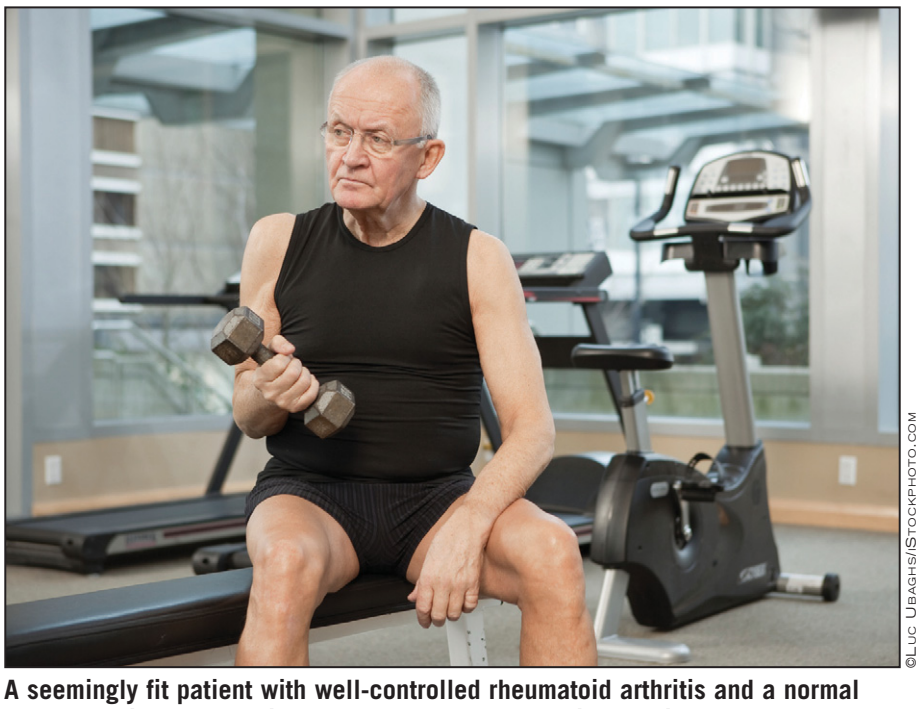
MARINA DEL REY, CALIF. — Rheumatoid arthritis patients with well-controlled disease may benefit from performing fat-burning exercises accompanied by resistance training—such as weight lifting—to preserve or even build muscle mass, according to Dr. Joan M. Bathon.

Such a regimen has the potential to address some of the elevated risks for cardiovascular disease found in this population.

A seemingly fit patient with well-controlled rheumatoid arthritis (RA) and a normal body mass index may still have excess body fat, elevated C-reactive protein levels, and increased coronary artery disease risk.

There is no easy way to assess body composition in the office. And even when body mass index is considered, "you don't know how healthy" an RA patient is, said Dr. Bathon, who is professor of medicine and director of the Johns Hopkins Arthritis Center in Baltimore.

The chronic inflammation of RA can waste muscles, and RA-associated disability can promote sedentary lifestyles, which in turn leads to excess fat. Sometimes muscle loss is offset by fat gain, leaving a patient with a normal or even low BMI, yet with an unhealthy body composition, Dr. Bathon explained at a rheumatology seminar that was sponsored by the University of California, Los Angeles.



©LUC UBAGHS/ISTOCKPHOTO.COM

**A seemingly fit patient with well-controlled rheumatoid arthritis and a normal body mass index may still have a number of heart disease risk factors.**

Appendicular fat correlates with disability, and visceral fat correlates with coronary artery disease, the leading killer of patients with RA, she said.

When patients have well-controlled RA, their high C-reactive protein levels might be coming not from the inflamed joints, but rather from fat deposits, and might signal an increased risk of coronary artery disease.

Dr. Bathon reported supportive data from a published study.

She and her colleagues performed anthropomorphic measurements and dual-energy x-ray absorptiometry (DXA) scanning to assess fat:muscle ratio in 72 men and 117 women with RA and moderate disability. A single CT image of the abdomen in the axial plane was used to assess the amount of visceral fat. The subjects were then matched with 189 healthy controls.

Compared with the healthy controls, women with rheumatoid arthritis who had BMIs below 25 kg/m$^2$ or between 25 and 30 were more likely than controls to have sarcopenic obesity (defined as too little muscle and too much fat). The men with RA had increased levels of visceral fat.

Abnormal body composition was associated with increases in joint deformity, self-reported disability scores, C-reactive protein levels, rheumatoid factor seropositivity, and a lack of current treatment with disease-modifying antirheumatic drugs (Arthritis Rheum. 2008;59:807-15). ■

***Disclosures:*** *Dr. Bathon said that she had no relevant conflicts.*