Reducing Life-Threatening Allopurinol Hypersensitivity

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**Allopurinol is the cornerstone** of pharmacologic urate-lowering therapy for recurrent gouty arthritis. Although this drug is inexpensive and efficacious, it may cause rare, but life-threatening, cutaneous drug eruptions: the allopurinol hypersensitivity syndrome.1 Mortality rates for individuals experiencing allopurinol hypersensitivity can exceed 30% and long-term morbidity is common.2 In this issue of *JAMA Internal Medicine*, Yang et al2 demonstrate that in Taiwan, both allopurinol prescribing and hypersensitivity reactions are on the rise. Their findings highlight the value of judicious, guideline-based hyperuricemia management throughout the world.

The authors used a retrospective cohort design to investigate the incidence and predictors of allopurinol hypersensitivity among almost every Taiwanese adult during a 6-year period. Using insurance claims, they found that the incidence of allopurinol prescribing and hypersensitivity increased over time, with an overall allopurinol hypersensitivity incidence of 0.4% among new users, 8.3% of whom died from the drug reaction. Hypersensitivity reactions were more likely among new users with chronic kidney disease or cardiovascular disease who received allopurinol for asymptomatic hyperuricemia as opposed to symptomatic gout; these patients represented 49.5% of new user prescriptions by the end of the study period.

In the United States, allopurinol hypersensitivity occurs one-fourth as often as Yang et al2 found in Taiwan. This lower incidence is in part a matter of genetic epidemiology: the HLA-B*5801 haplotype is strongly associated with allopurinol hypersensitivity and is prevalent in Han Chinese individuals, and the population of Taiwan is 95% Han Chinese.3 Nevertheless, millions of allopurinol prescriptions are dispensed in US ambulatory settings annually. How do we prevent allopurinol hypersensitivity in our ethnically diverse population? Febuxostat, the newer alternative available only as the proprietary formulation, is not associated with the same hypersensitivity reactions as allopurinol. However, transitioning therapy to febuxostat for millions of patients is not cost-effective.4

The findings of Yang et al2 are an important reminder that we should follow the American College of Rheumatology’s guidelines.1 First, begin gout management with lifestyle changes and prescribe urate-lowering therapy only for individuals with frequent gout attacks (>2 per year), tophaceous gout, comorbid stage 2 to 5 chronic kidney disease, or urolithiasis. Allopurinol should not be prescribed for asymptomatic hyperuricemia. Second, all Thai and Han Chinese patients, as well as Korean patients with kidney disease, should be screened for the HLA-B*5801 haplotype prior to allopurinol initiation. If the results of the test are positive or the patients are otherwise at high risk, consider an alternative agent. Finally, start allopurinol therapy at no more than 100 mg/d and titrate the dose slowly.

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