Allopurinol hypersensitivity syndrome

Wid Yaseen MD, Bourne Auguste MD MSc, Jonathan Zipursky MD PhD

■ Cite as: *CMAJ* 2023 April 3;195:E483. doi: 10.1503/cmaj.221575

1 Allopurinol hypersensitivity syndrome (AHS) is a severe adverse drug reaction

Allopurinol hypersensitivity syndrome includes Stevens–Johnson syndrome, toxic epidermal necrolysis and drug reaction with eosinophilia and systemic symptoms. It affects about 1 in 1000 patients prescribed allopurinol, and reported mortality is between 20% and 25%.[1] Patients typ-ically present with an exanthem (e.g., morbilliform eruption, erythema multiforme or exfoliative dermatitis), renal impairment, liver injury and eosinophilia. The syndrome may occur within weeks to months of drug exposure, but most cases occur within 8–9 weeks.[2]

2 Guidelines recommend screening for the *HLA-B*58:01* allele in high-risk populations before starting allopurinol

Risk of AHS is nearly 100-fold higher in carriers of the *HLA-B*58:01* allele than in noncarriers.[3] Populations with high allele frequency include people of Han Chinese (6%–8%), Korean (12%) and Thai (6%–8%) descent.[3] Testing for the allele is widely available in Canada. In the absence of other risk factors, the risk of AHS is low in people with a negative test result for the *HLA-B*58:01* allele.[4]

3 Chronic kidney disease and cardiovascular disease are clinical risk factors for AHS

Population-based studies have shown an 11-fold increased risk of hospital admission for AHS in patients with chronic kidney disease and cardiovascular disease treated with high doses of allopurinol (> 100 mg/d).[5]

4 Starting low-dose allopurinol and titrating slowly might mitigate the risk of AHS

Although the relation between maintenance dose and AHS risk is controversial, allopurinol should be started at a low dose (≤ 100 mg/d) and lower (≤ 50 mg/d) in patients with stage 4 chronic kidney disease or higher.[1,2]

5 Treatment includes stopping allopurinol and supportive care

Systemic steroids and immunomodulatory therapies may be useful. Specific treatment depends on whether the patient has Stevens–Johnson syndrome, toxic epidermal necrolysis or drug reaction with eosinophilia and systemic symptoms. Patients who develop AHS should not be re-exposed to allopurinol; however, alternate urate-lowering therapies (e.g., febuxostat) can be considered.[1]

References

1. Khanna D, Fitzgerald JD, Khanna PP, et al.; American College of Rheumatology. 2012 American College of Rheumatology guidelines for management of gout. Part 1: systematic non-pharmacologic and pharmacologic therapeutic approaches to hyperuricemia. *Arthritis Care Res (Hoboken)* 2012;64:1431-46.
2. Stamp LK, Day RO, Yun J. Allopurinol hypersensitivity: investigating the cause and minimizing the risk. *Nat Rev Rheumatol* 2016;12:235-42.
3. Quach C, Galen BT. HLA-B*5801 testing to prevent allopurinol hypersensitivity syndrome: a teachable moment. *JAMA Intern Med* 2018;178(9):1260-1.
4. Hershfield MS, Callaghan JT, Tassaneeyakul W, et al. Clinical Pharmacogenetics Implementation Consortium guidelines for human leukocyte antigen-B genotype and allopurinol dosing. *Clin Pharmacol Ther* 2013;93(2):153-8.
5. Yokose C, Lu N, Xie H, et al. Heart disease and the risk of allopurinol-associated severe cutaneous adverse reactions: a general population–based cohort study. *CMAJ* 2019;191(39):E1070-7.

Competing interests: Bourne Auguste received speaking honoraria from Baxter Healthcare and Amgen, outside of the submitted work. Jonathan Zipursky received payments from private law firms for medico–legal opinions regarding the safety and effectiveness of drugs, outside of the submitted work. No other competing interests were declared.

This article has been peer reviewed.

Affiliations: Department of Medicine (Yaseen, Auguste, Zipursky), University of Toronto; Divisions of Nephrology (Auguste), and Clinical Pharmacology and Toxicology (Zipursky), Sunnybrook Health Sciences Centre, Toronto, Ont.

Correspondence to: Wid Yaseen, wid.yaseen@mail.utoronto.ca