Allopurinol for gout

Consider the case for limited HLA-B*5801 *screening*

Tim Tse, Bosco Wu, Sanjyot Vagholkar, Simon Willcock

THE INCIDENCE AND PREVALENCE of gout is increasing throughout the world, and general practitioners often provide initial management with the use of urate-lowering medications such as allopurinol.[1] Allopurinol, a xanthine oxidase inhibitor, reduces the conversion of hypoxanthine and xanthine to uric acid, and it constitutes up to 98% of the urate-lowering medications prescribed in Australia.[2] However, allopurinol can rarely cause severe cutaneous adverse reactions (SCAR) and allopurinol hypersensitivity syndrome (AHS). Estimated risks of developing SCAR from allopurinol range from 1:250 to 1:1000, with mortality rates of up to 25%.[1,3,4] Given the potentially serious consequence from such a commonly prescribed long-term medication, we outline the rationale behind opportunistic *HLA-B*5801* screening in patients with gout in high-risk groups prior to initiating allopurinol to reduce the incidence of SCAR and AHS.[5–7]

SCAR includes Stevens–Johnson Syndrome (SJS), toxic epidermal necrolysis (TEN) and drug reaction with eosinophilia and systemic symptoms (DRESS). Allopurinol is the leading medication-related cause of SJS/TEN in many countries around the world.[3] AHS, a life-threatening condition, manifests as a combination of rash, renal dysfunction, hepatocellular injury, fever, eosinophilia and leucocytosis. Treatment of these syndromes is based on immediate removal of the offending agent, supportive care and use of immunomodulators such as corticosteroids. A systematic review of all published cases of allopurinol hypersensitivity between 1950 and 2012 found 90% of patients developed reactions within 60 days of initiating allopurinol, and with a median of three weeks and mean 10 weeks. Of patients tested for *HLA-B*5801* following allopurinol hypersensitivity, 99% were positive, with 89% of Asian descent.[8]

*HLA-B*5801* is strongly associated with allopurinol-induced SCAR, especially in particular ethnic populations. A meta-analysis examining the likelihood of having *HLA-B*5801* in patients with SJS/TEN revealed a pooled diagnostic odds ratio (DOR) of 83.5 (95% confidence interval: 50.7, 137.4). The DOR compares the odds of a patient with SJS/TEN having *HLA-B*5801* with the odds of a patient without SJS/TEN having *HLA-B*5801*. Subgroup analyses revealed Han Chinese people had a significantly higher association (DOR: 196.1) when compared with Europeans (DOR: 58.4). The increased association is likely due to the higher *HLA-B*5801* allele frequencies in Southeast Asians: Singaporean Chinese 20.1%, Taiwanese 20.0%, Indian 15.4%, Hong Kongese 14.2%, Chinese 13.6% and Korean 12%, compared with those of European descent 1–5%.[3,4] *HLA-B*5801* has the characteristics of a good screening test to prevent SJS/TEN because of its high sensitivity (78.4%), specificity (96.2%) and negative predictive value (99%).[3] It is important to note that it is possible to have allopurinol-induced SCAR without being a carrier of *HLA-B*5801*.[4]

Worldwide guidelines addressing screening of patients for *HLA-B*5801* prior to the initiation of allopurinol are presented in Table 1. The American College of Rheumatology recently updated their recommendations in 2020, now conditionally recommending testing in patients of Southeast Asian descent or African Americans.[5] This builds on the 2012 guidelines, which recommended considering testing in patients at elevated risk: Han Chinese, Thai or Koreans with Stage III–V kidney disease.[6] The 2017 European League Against Rheumatism guidelines recommend screening to be left to the discretion of the treating doctor, who should be aware of the risks of severe allergic reaction if the patient is an *HLA-B*5801* carrier. The task force noted that it lacked data to make recommendations for cost-effective population-based screening given that the ethnicity demographics in Europe are dissimilar to that of the high-risk Asian cohort.[7] The high-risk populations identified in these guidelines are particularly relevant in Australia given

that the Australian population is 5.2% Chinese and 0.5% Korean ancestry. In major capital cities such as Sydney, the population with Chinese ancestry increases to 10%.[9]

The Clinical Pharmacogenetics Implementation Consortium recommend that if a single *HLA-B*5801* allele is present on screening, allopurinol is contraindicated in favour of alternative urate-lowering medications such as probenecid or febuxostat.[1]

Use of *HLA-B*5801* in screening has been evaluated in a 2015 prospective cohort study in Taiwan. A total of 2926 patients who required allopurinol therapy were recruited. Prior to initiation of allopurinol, patients were tested for *HLA-B*5801*; if positive, they were given alternative therapy. Of the participants, 19.6% tested positive to *HLA-B*5801*. Following a minimum follow-up period of nine months, none of the 571 participants with *HLA-B*5801* who were given alternative therapy developed any SCAR. The study authors concluded that on the basis of historical incidence data, an estimated seven cases of allopurinol-induced SCAR were avoided in a cohort of that size.[10]

Although rare, allopurinol-induced SCAR and AHS have significant morbidity and mortality consequences. The presence of *HLA-B*5801* is significantly associated with these adverse conditions occurring, and worldwide guidelines recommend or suggest the practitioner to consider an individualised approach to screening in patients from high-risk groups. The multicultural Australian population has a high proportion of these high-risk groups (Han Chinese/Korean), particularly in capital cities. Australian general practitioners should consider the evidence for limited *HLA-B*5801* screening of patients from these populations and be aware of the potential medication-induced side effects when prescribing allopurinol.

Authors

Tim Tse BMed, MD, MMed, FRACGP, General Practitioner, Department of Primary Care, Macquarie University, Macquarie Park, NSW

Bosco Wu MBBS, BMedSci (Hons), FRACGP, General Practitioner, Department of Primary Care, Macquarie University, Macquarie Park, NSW

Sanjyot Vagholkar MBBS (Hons), MPH, PhD, FRACGP, General Practitioner, Professor, Department of Primary Care, Macquarie University, Macquarie Park, NSW

Simon Willcock MBBS, PhD, FRACGP, General Practitioner, Professor, Department of Primary Care, Macquarie University, Macquarie Park, NSW

Competing interests: None.

Funding: None.

Provenance and peer review: Not commissioned, externally peer reviewed.

Correspondence to:
tim.tse@mqhealth.org.au

References

1. 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):153–58. doi: 10.1038/clpt.2012.209.
2. Chung Y, Lu CY, Graham GG, Mant A, Day RO. Utilization of allopurinol in the Australian community. Intern Med J 2008;38(6):388–95. doi: 10.1111/j.1445-5994.2008.01641.x.
3. Yu KH, Yu CY, Fang YF. Diagnostic utility of *HLA-B*5801* screening in severe allopurinol hypersensitivity syndrome: An updated systematic review and meta-analysis. Int J Rheum Dis 2017;20(9):1057–71. doi: 10.1111/1756-185X.13143.
4. Stamp LK, Barclay ML. How to prevent allopurinol hypersensitivity reactions? Rheumatology (Oxford) 2018;57(suppl_1):i35–i41. doi: 0.1093/rheumatology/kex422.
5. FitzGerald JD, Dalbeth N, Mikuls T, et al. 2020 American College of Rheumatology Guideline for the management of gout. Arthritis Care Res (Hoboken) 2020;72(6):744–60. doi: 10.1002/acr.24180.
6. Khanna D, Fitzgerald JD, Khanna PP, et al. 2012 American College of Rheumatology Guidelines for management of gout. Part 1: Systematic nonpharmacologic and pharmacologic therapeutic approaches to hyperuricemia. Arthritis Care Res (Hoboken) 2012;64(10):1431–46. doi: 10.1002/acr.21772.
7. Richette P, Doherty M, Pascual E, et al. 2016 updated EULAR evidence-based recommendations for the management of gout. Ann Rheum Dis 2017;76(1):29–42. doi: 10.1136/annrheumdis-2016-209707.
8. Ramasamy SN, Korb-Wells CS, Kannangara DR, et al. Allopurinol hypersensitivity: A systematic review of all published cases, 1950–2012. Drug Saf 2013;36(10):953–80. doi: 10.1007/s40264-013-0084-0.
9. Australian Bureau of Statistics. 2016 Census Community Profiles. Belconnen, ACT: ABS, 2016. Available at www.abs.gov.au/census/find-census-data/community-profiles/2016/0 [Accessed 17 October 2017].
10. Ko TM, Tsai CY, Chen SY, et al. Use of *HLA-B*58:01* genotyping to prevent allopurinol induced severe cutaneous adverse reactions in Taiwan: National prospective cohort study. BMJ 2015;351:h4848. doi: 10.1136/bmj.h4848.

Table 1. Summary of guidelines regarding *HLA-B*5801* testing prior to initiation of allopurinol

Guideline	Year	Recommendation
American College of Rheumatology[5]	2020	Conditionally recommend testing *HLA-B*5801* before starting allopurinol in patients of Southeast Asian descent (eg Han Chinese, Korean, Thai) and for African American patients
European League Against Rheumatism[7]	2017	Screening for *HLA-B*5801* left to the discretion of the treating doctor
American College of Rheumatology*[6]	2012	Consider *HLA-B*5801* before starting allopurinol in selected patients with elevated risk Elevated risk includes Korean descent with Stage III or worse chronic kidney disease, Han Chinese or Thai

**The American College of Rheumatology Guidelines were updated in 2020.*

correspondence **ajgp@racgp.org.au**