

HLA-B*5801 testing: Is it time to consider mandatory testing prior to prescribing allopurinol in Singapore?

Dear Editor,

Stevens-Johnsons Syndrome (SJS) and Toxic Epidermal Necrolysis (TEN) are severe, life-threatening mucocutaneous reactions that most commonly occur as drug-related reactions.¹ In recent years, several risk factors for the development of SJS/TEN, such as genetic factors, have been identified. Notably, carriers of the HLA-B*5801 and HLA-B*1502 alleles have an increased risk of SJS/TEN with the use of allopurinol and carbamazepine, respectively.² Consequently, much debate has arisen over the utility of pharmacogenomics in preventing SJS/TEN. We will discuss the evidence surrounding genetic testing in the prevention of allopurinol-induced SJS/TEN, with the aim of highlighting the potential value of pre-testing.

In Singapore, the number of cases of allopurinol-induced severe cutaneous adverse reactions (SCAR) remains high. A total of 131 cases of allopurinol-related SCAR were reported across the past decade (2013–2022), of which 63 were SJS/TEN cases. These incidents were in contrast to carbamazepine-related SCAR, which had 31 cases in the same time period (2013–2022), of which 19 were SJS/TEN. A clear decline in the number of carbamazepine-related SJS/TEN cases was seen since the mandatory HLA-B*1502 testing prior to carbamazepine initiation was introduced in 2013. Currently, the HLA-B*5801 testing prior to allopurinol initiation is not mandatory in Singapore. Reasons cited for this decision include the low positive predictive value (1.52%) compared to the high prevalence of the allele in our population (18.5%) and the lack of cost-effectiveness of testing.³ Others have argued that although the HLA allele plays a central role in allopurinol-related SJS/TEN, it may not be the only factor required for its occurrence.⁴

Nonetheless, we believe there is value in HLA pre-testing. First, there is a need to relook at the data on the cost-effectiveness of testing. The current data cite the cost of testing and the higher cost of alternative urate-lowering therapies as the main drivers of the increased cost of universal HLA-B*5801 testing. However, most cost-effectiveness models are unable to account for the potentially significant morbidity and long-term multi-systemic sequelae of SJS/TEN. While local

studies have attempted to examine long-term costs of SJS/TEN, these were limited to ocular complications of dry eye syndrome in both studies.^{3,5} Statistics used in these studies were also based on incidence data in other countries, which may not be an accurate representation of the Singapore context. These are important considerations as such complications can lead to a substantial increase in costs. For example, a study on healthcare costs of the disease found that SJS and TEN resulted in significantly prolonged lengths of stay at approximately 9.8 days and 16.5 days, respectively, as well as higher costs of care at approximately USD21,437 and USD53,695 (approx. SGD28,718 and SGD71,932), respectively, in comparison to all other admissions (average length of stay at 4.7 days and cost at USD11,281 [approx. SGD15,113]).⁶ Chiu et al. also found that patients with SJS/TEN tend to suffer a substantial loss of life expectancy and high lifetime healthcare expenditure compared to the general population.⁷

Second, cost-effectiveness studies are based on the assumption of appropriate prescription of allopurinol for the treatment of gout. However, inappropriate use of allopurinol, such as for infrequent gout attacks and asymptomatic hyperuricemia, remains prevalent in Singapore.⁸ This is a universal issue where poor compliance to these standards of care are commonly seen in other published studies as well.⁹ Although potentially remediable, allopurinol continues to be prescribed inappropriately despite efforts from the Health Sciences Authority, who have released numerous newsletters and guidelines on allopurinol prescription. This calls for a stronger safeguard in place to help reduce prescription of allopurinol, especially in cases where it is not indicated.

In addition, there is promising evidence on the utility of HLA testing. A study by Ko et al. demonstrated a reduction in the incidence of allopurinol-induced SCAR with the implementation of pre-testing in Taiwan, a country with a high incidence of the allele (reported to be up to 20%). The study results suggested that HLA-B*5801 pre-testing could potentially prevent an estimated number of 330 cases of allopurinol-induced SCAR per year.¹⁰ Similarly, studies in Korea, China and Thailand also demonstrated a reduced incidence of SCAR with pre-testing in patients with chronic

kidney disease (CKD).^{1,2,4} Furthermore, these studies also demonstrated the cost-effectiveness of pre-testing in such patients. For example, Wong et al. found that pre-testing in patients with renal impairment could potentially reduce healthcare costs by up to 67.1%, where the total cost of hospitalisation of SCAR patients amounted up to 3 times higher than performing HLA pre-testing itself.⁴ Park et al. also found that treatment informed by HLA-typing in CKD patients cost USD138 (approx. SGD185) less than the conventional treatment and was also associated with a higher likelihood of continued gout treatment without SCARs.² Given that this patient group has a 5-fold risk of developing SCARs, effective preventative measures are of paramount importance. Hence, as a first step towards universal HLA pre-testing, it may be prudent to consider implementing testing in selected patient groups at higher risk of developing SCARs, such as CKD patients.

Although HLA-B*5801 screening will limit the use of allopurinol as a first-line medication in patients with the allele, several alternatives with a lower SCAR risk profile remain available, such as probenecid, benzbromarone and febuxostat. While febuxostat had been previously plagued with concerns over cardiovascular safety, the Febuxostat versus Allopurinol Streamlined Trial (FAST) published in 2020 demonstrated no increased risk of cardiovascular events or mortality compared to allopurinol. Greater awareness on the use of these alternative therapeutics will increase clinicians' confidence in HLA pre-testing.

In conclusion, allopurinol remains an important and potentially preventable cause of SCAR. Given the significant morbidity and potential mortality of allopurinol-related SCAR, it may be time to re-examine current data and reconsider the amendment of recommendations on HLA-B*5801 testing. Genetic testing before allopurinol initiation may be able to potentially act as a safeguard and prevent unnecessary prescription. On the other hand, future studies could consider exploring the development of guidelines regarding treatment alternatives for patients at high risk of allopurinol-related SCAR, and to personalise the treatment of gout based on test results and patient factors.

Declarations

The authors do not have any affiliations or financial involvement with any commercial organisations with a direct financial interest in the subject or materials discussed in the manuscript.

Acknowledgement

The authors would like to acknowledge Ms Celine Loke (Health Sciences Authority, Singapore) for providing statistics on cases of severe cutaneous adverse reactions for this manuscript.

Keywords: dermatology, drug reactions, internal medicine, pharmacogenomics, public health

REFERENCES

1. Saokaew S, Tassaneeyakul W, Maenthaisong R, et al. Cost-effectiveness analysis of HLA-B*5801 testing in preventing allopurinol-induced SJS/TEN in Thai population. *PLoS One* 2014;9:e94294.
2. Park DJ, Kang JH, Lee JW, et al. Cost-effectiveness analysis of HLA-B5801 genotyping in the treatment of gout patients with chronic renal insufficiency in Korea. *Arthritis Care Res (Hoboken)* 2015;67:280-7.
3. Dong D, Tan-Koi WC, Teng GG, et al. Cost-effectiveness analysis of genotyping for HLA-B*5801 and an enhanced safety program in gout patients starting allopurinol in Singapore. *Pharmacogenomics* 2015;16:1781-93.
4. Wong CSM, Yeung CK, Chan CY, et al. HLA-B*58:01 screening to prevent allopurinol-induced severe cutaneous adverse reactions in Chinese patients with chronic kidney disease. *Arch Dermatol Res* 2022;314:651-9.
5. Pruis SL, Jeon YK, Pearce F, et al. Cost-effectiveness of sequential urate lowering therapies for the management of gout in Singapore. *J Med Econ* 2020;23:838-47.
6. Hsu DY, Brieve J, Silverberg NB, et al. Morbidity and Mortality of Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis in United States Adults. *J Invest Dermatol* 2016;136:1387-97.
7. Chiu YM, Chiu HY. Lifetime risk, life expectancy, loss-of-life expectancy, and lifetime healthcare expenditure for Stevens-Johnson syndrome/toxic epidermal necrolysis in Taiwan: follow-up of a nationwide cohort from 2008 to 2019. *Br J Dermatol* 2023;189:553-60.
8. Lee HY, Tay LK, Thirumoorthy T, et al. Cutaneous adverse drug reactions in hospitalised patients. *Singapore Med J* 2010;51:767-74.
9. Pasina L, Brucato AL, Djade CD, et al. Inappropriate prescription of allopurinol and febuxostat and risk of adverse events in the elderly: results from the REPOSI registry. *Eur J Clin Pharmacol* 2014;70:1495-503.
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.

Felicia Li Ling Ong¹ MBBS,
Shiu Ming Pang^{1,2} MBBS

¹ Department of Dermatology, Singapore General Hospital

² Duke-NUS Medical School

Correspondence: Clin. A/Prof Shiu Ming Pang, 20 College Road, Department of Dermatology, Level 4, Academia, Singapore General Hospital, Singapore 169856. Email: pang.shiu.ming@singhealth.com.sg