

Purpose of this document: Outlines important actions to prevent allopurinol-induced severe cutaneous adverse reactions (SCAR) and associated mortality in select ethnic groups and mitigate this risk in other populations. This is a missed opportunity in our local practice.¹

Risk of SCAR, mortality and timeline:



- 0.3% incidence of allopurinol-induced severe cutaneous adverse reactions e.g. Stevens-Johnson Syndrome (SJS), Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS), Toxic Epidermal Necrolysis (TEN) in at risk ethnic groups (Koreans with CKD Stage 3 or greater, Han Chinese or Thai) due to presence of HLA-B*58:01 allele and its' strong association with SCAR.^{2,3,4}
- There is some dose dependency (affected by renal function, drug-drug interactions).
- TEN has a mortality rate of 25% or greater.^{1,4}
- Reactions can occur within 2 to 8 weeks of starting allopurinol.⁵

Possible mechanism of toxicity

1. Active allopurinol metabolite (oxypurinol) leads to dose-dependent activation of cytotoxic T cells. The risk of this activation is much higher if HLA-B*58:01 is present.^{6,7}
2. Risk may be increased with **impaired renal function** leading to accumulation of oxypurinol or drugs that can interfere with oxypurinol clearance (e.g. thiazides).⁷
3. Therefore allopurinol should be **at the lowest starting dose adjusted for renal dysfunction, with any thiazides stopped.**⁵

6 STEPS TO PREVENT OR MITIGATE SCAR

1. Consider ethnic group to order testing for patients at high risk of having HLA-B*5801:



Presence of this allele strongly increases risk for developing allopurinol-induced severe-cutaneous reaction.^{3,4,6} The American College of Rheumatology recommend to consider testing for HLA-B*58:01 prior to prescribing allopurinol in Koreans with CKD Stage 3 disease or greater, Han Chinese or Thai, due to increased frequency of this allele in these populations.^{3,4,6} Given that ~80% of mainland Chinese and more than 95% of Taiwanese are of Han ethnicity, genetic testing is recommended for all patients of Chinese/Taiwanese ethnicity.

Frequency of HLA-B*58:01 allele:

Population	Approximate HLA-B*58:01 Allele Frequency (%)	Recommendation for testing prior to allopurinol initiation
Han Chinese descent	6.0-8.0	Consider with any renal function
Thai descent	6.0-8.0	Consider with any renal function
Korean descent (with CKD Stage 3 or worse)	12.0	Consider in CKD stage 3 or worse



How to order HLA-B*58:01:

- **Accessible via any laboratory in British Columbia**
- Need to indicate: "query allopurinol sensitivity"
- Results should be reported within 4 weeks

Interpreting HLA-B*58:01 tests:

Result	Defined as	Implications	Predictive value
Positive	At least one copy of HLA-B*58:01 detected	Significantly increased risk of allopurinol-induced SCAR*	Positive predictive value = ~1.5%
Negative	NO copies of HLA-B*58:01 detected	Very low risk of allopurinol-induced SCAR*	Negative predictive value = 100% in Taiwanese Han population. ⁴

*severe cutaneous adverse reaction

2. Prescribe depending on HLA-B genotype:



Genotype	Recommendation
Negative for HLA-B*58:01	Start allopurinol at 100 mg PO daily if CrCl above 30 mL/min*
Positive for HLA-B*58:01	Alternative therapy is recommended. (e.g. febuxostat 40 mg PO daily; Note PharmaCare special authority required)

3. Adjust for renal dysfunction and start low dose:

For patients with CKD \geq Stage 4 (CrCl \leq 30 mL/min), recommended starting dose is 50 mg once daily. Dose may be gradually increased to achieve desired serum uric acid level.⁸ See www.rheumatology.org

4. Stop thiazide diuretics:

Due to an increased risk of accumulation and development of severe toxicity, thiazides should be avoided in patients with gout if possible and especially with concurrent allopurinol use.⁵

5. Advise to stop allopurinol at first sign of a rash and see a doctor

6. Confirm patient understanding by asking open-ended questions:

“What would need to happen for you to stop taking this medication” ... “Which medications have just changed”?

Summary of Key Actions to Prevent or Mitigate Allopurinol Severe Cutaneous Adverse Reactions:

1. TEST HLA-B*58:01 status if Korean (with CKD Stage 3 or greater), Chinese or Thai
2. PRESCRIBE depending on genotype
3. ADJUST for renal dysfunction and start LOW dose
4. STOP any thiazide diuretic
5. ADVISE to STOP allopurinol at first signs of skin rash, SEE A DOCTOR
6. CONFIRM patient’s understanding of what to do if rash develops and any medication changes

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