FPIN's Clinical Inquiries

Should Allele Testing Be Done Before Prescribing Allopurinol to Prevent Severe Cutaneous Adverse Reactions?

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Clinical Question

Should allele testing be done before prescribing allopurinol to prevent severe cutaneous adverse reactions (SCARs) such as Stevens-Johnson syndrome, toxic epidermal necrolysis, and drug reaction with eosinophilia and systemic symptoms?

Evidence-Based Answer

Moderate evidence supports allele testing for HLA-B*58:01 before initiating allopurinol to decrease the incidence of SCARs in higher risk populations. (Strength of Recommendation [SOR]: B, based on systematic review and meta-analysis of population-controlled studies, prospective cohort studies.) Patient populations who are not at increased risk should not be screened. (SOR: C, based on consensus recommendation.)

Evidence Summary

A 2015 nonrandomized prospective cohort study (n = 2,926) evaluated the use of prospective genotyping for HLA-B*58:01 before initiation of allopurinol to prevent SCARs, including Stevens-Johnson syndrome, toxic epidermal necrolysis, drug reaction with eosinophilia and systemic symptoms, and others.[1] Historical incidence was used for the control group. The study included 15 medical centers in various regions across Taiwan from July 2009 to August 2014. Exclusion criteria included individuals who had a history of allopurinol-induced hypersensitivity, had a history of bone marrow transplant, or were not of self-described Han Chinese descent. HLA-B*58:01 genotyping with real-time polymerase chain reaction was performed before starting treatment with allopurinol for all patients, and all patients were counseled on SCARs, with HLA-B*58:01-positive patients (n = 571) being recommended alternative treatments and non-carriers (n = 2,339) being started on allopurinol. The mean estimated historical incidence of allopurinol-induced SCARs in the control group from 2001 to 2004 was 0.30% per year (95% CI, 0.28% to 0.31%). This range of years was used to prevent confounding with early adopters of pretreatment genotyping. This study had a sufficient number of patients for a power of 86% to detect a reduction of allopurinol-induced SCARs from 0.30% per year to 0.03%. None of the study participants were diagnosed with SCARs, a significant difference (two-tailed *P*; *P* = .0026) compared with historical incidence, which predicted seven occurrences of SCARs.

A 2018 nonrandomized prospective study of 542 patients from 10 Korean hospitals evaluated the usefulness of screening for the HLA-B*58:01 allele to identify at-risk individuals for allopurinol-induced SCARs.[2] The patients had chronic renal insufficiency, defined as a glomerular filtration rate of less than 60 mL per minute for at least three months, with concurrent hyperuricemia, and each was genotyped

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for the HLA-B*58:01 allele. Of the enrolled patients, 503 were negative and treated with allopurinol at appropriate renal dosing, and 39 were HLA-B*58:01 allele positive and were treated with the alternative medication, febuxostat (Uloric), at appropriate renal dosing. The enrolled patients were compared in a retrospective manner with the historical incidence of SCARs in 4,002 matched patients from the same hospitals. Patients were followed biweekly for 90 days using phone surveys. Patients who withdrew consent or stopped allopurinol therapy were excluded from the analysis. A two-sided, one-sample binomial test was used to compare the prospective study and the historical control data with two-tailed *P* values. One of the 39 HLA-B*58:01 allele-positive and 52 of the negative patients withdrew consent or were lost to follow-up. None of the participants in this study developed SCARs, and 38 cases of SCARs were identified in the historical control patients (0% vs. 0.95%; $P = .029$).

A 2011 systematic review and meta-analysis included six studies for analysis—three case-control studies, two case-population studies, and one retrospective cohort study.[3] The primary outcome of this analysis was the carrier frequency of HLA-B*58:01 in allopurinol-induced cases of Stevens-Johnson syndrome and toxic epidermal necrolysis compared with each control group. Studies included patients self-identified as Han Chinese, Thai, Japanese, Korean, and mixed European populations, including patients self-described as South American, African, Asian, and European. Four studies were included in a pooled quantitative analysis—total HLA-B*58:01 carriers were 54 of 55 among case patients and 74 of 678 among the control patients. The pooled odds ratio for allele carriers developing Stevens-Johnson syndrome or toxic epidermal necrolysis was 96.6 (95% CI, 24.5 to 381.0). Five studies were included in a separate analysis that compared patients with the HLA-B*58:01 genotype and allopurinol-induced cases of Stevens-Johnson syndrome and toxic epidermal necrolysis with the general population. HLA-B*58:01 carrier frequency was 72.5% (50 of 69) for case patients and 5% (171 of 3,378) for population control patients. This group of studies had a pooled odds ratio of 79.3 (95% CI, 41.5 to 151.4). A subgroup analysis of populations of both allele-positive self-described Asian and self-described non-Asian cohorts revealed a statistically significant association between allopurinol-induced Stevens-Johnson syndrome and toxic epidermal necrolysis for both cohorts, with an odds ratio of 74.2 (95% CI, 27.0 to 204.1) and 101.5 (95% CI, 45.0 to 228.8), respectively, indicating a broader utility to allele testing to prevent SCARs in HLA-B*58:01 carriers.

Recommendations from Others

The 2020 update to the American College of Rheumatology Guideline for the Management of Gout conditionally recommends HLA-B*58:01 allele testing before initiating allopurinol for patients of reported Southeast Asian and African American descent and recommends against testing other patient populations.[4] A 2017 study demonstrated cost-effectiveness of allele testing in populations reportedly at increased risk, including in the United States.[5]

A recent article published in the *Journal of the American Medical Association* points out problems associated with comparing HLA frequencies across racial, ethnic, or geographic groups, particularly variability in sample size and sampling methods and inconsistent use of racial and geographic categories.[6] Studies suggest that the genetic variation in the allele within a country can often be as great or greater than between countries or ethnic populations. This is a limitation of the American College of Rheumatology recommendation to confine testing to certain ethnic groups.

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