Allopurinol pharmacogenetics: assessment of potential clinical usefulness

Use of pharmacogenetics to inform treatment decisions remains a priority for clinicians, patients and public health agencies. We previously developed a framework for systematically assessing whether pharmacogenetic test information would likely bring value to clinical decision-making and enjoy practical uptake. We applied this tool to allopurinol to determine potential usefulness of *HLA* genetic information in assessing risk for allopurinol-induced severe cutaneous adverse reactions. We quantified allopurinol use data and the magnitude of adverse event signals using US FDA databases, reviewed reported cases of allopurinol-associated severe cutaneous adverse reactions to assess whether clinical subtypes of patients could be identified, performed pooled analyses of associations between *HLA* variation and allopurinol-induced severe cutaneous adverse reactions and described considerations in clinical implementation of allopurinol pharmacogenetics.

KEYWORDS: adverse reaction ▪ allopurinol ▪ *HLA-B*5801* ▪ safety ▪ SCAR ▪ Stevens–Johnson syndrome ▪ US FDA

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The use of clinical and genetic information to make informed treatment decisions remains a high priority for clinicians, patients and public health agencies such as the US FDA. While barriers to widespread clinical uptake of pharmacogenetics exist, there are also enabling factors that allow for the use of pharmacogenetic-enhanced therapeutic decisions in some cases. We previously developed a framework for systematically considering whether information from a given pharmacogenetic test would be likely to bring value to clinical decision-making and enjoy practical uptake [1]. This framework, known as the 'pharmacogenetic pyramid', was developed as a series of question-based assessments to gauge potential usefulness of pharmacogenetics in such diverse applications as clinical guideline development, FDA drug label-update considerations and clinician determination as to the utility of such test information in their individual practices.

The specific questions asked in this framework included:

- What is the medical need for the pharmacogenetic test?
- What is the strength of the pharmacogenetic association?
- What are the nongenetic, clinical variables that can help focus pharmacogenetic testing on a particularly 'at-risk' population?
- What is the clinical course of action once test results are known (i.e., is the information medically 'actionable')?

Some decision-makers may also be interested in a fifth question; namely, what are the cost considerations of testing (although the multidimensionality of health technology valuation makes it beyond the scope of this paper)? We applied the pharmacogenetic pyramid assessment tool to allopurinol, a commonly prescribed agent for the treatment of gout, to determine the potential usefulness of pharmacogenetic test information in assessing risk for potentially life-threatening allopurinol-induced severe cutaneous adverse reactions (SCAR), such as Stevens–Johnson syndrome (SJS), toxic epidermal necrolysis (TEN) and other hypersensitivity syndromes. Specifically, we:

- Quantified allopurinol drug use data and the magnitude of the adverse event signal for allopurinol using FDA databases;
- Reviewed reported cases of allopurinol-associated SCAR to determine whether clinical subtypes of patients reporting SCAR could be identified;
- Performed pooled analyses of the association between *HLA* gene variation and allopurinol-induced SCAR;
- Describe several considerations in the potential clinical implementation of allopurinol pharmacogenetics.

Question 1. What is the medical need for the genetic test?

One must, in part, consider the size of the potential population exposed to the drug of interest

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and the risk of the adverse event in exposed populations to determine whether there is a potential medical need for pharmacogenetic test information to guide treatment decisions. To that end, we queried proprietary drug use databases licensed by the FDA to obtain outpatient drug utilization information and estimates of the total number of prescriptions dispensed for allopurinol by age and sex. Data compiled from SDI Vector One®: National was used to examine outpatient retail utilization patterns for projected dispensed prescriptions from 1 January 2002 to 31 October 2009.

For the entire review period, over 81 million total prescriptions were dispensed in outpatient retail pharmacy settings for allopurinol. Overall, prescription utilization increased by approximately 47% from 2002 to 2008. By year 2008, total dispensed prescriptions for allopurinol reached its highest point at approximately 12 million prescriptions. Male patients accounted for approximately 59 million total prescriptions (~72%). From year 2002 to 2008, the number of prescriptions dispensed for males and females increased by approximately 44 and 53%, respectively.

Among the selected age and gender bands, male patients over 71 years of age accounted for the greatest proportion of dispensed prescriptions for allopurinol products with approximately 16 million dispensed prescriptions (~20%), followed by male patients 51–60 years of age with approximately 15 million dispensed prescriptions (~19%). Between the years 2002–2008, the number of prescriptions dispensed to male patients over 71 years of age compared with 51–60 years of age increased by approximately 58 and 34%, respectively. These data, in sum, suggest a relatively wide use of allopurinol.

The routine use of allopurinol for managing gout is largely driven by clinical practice recommendations as first-line therapy [2,3]. The FDA-approved allopurinol product label recommendations for gout control/lowering of uric acid is to start at 100 mg daily with a weekly uptitration to a maximal daily dose of 800 mg daily, until the target uric acid concentrations are less than 6.0 mg/dl. Despite these recommendations, it is well-documented that allopurinol is commonly underdosed in clinical practice with the majority of prescriptions being filled for 300 mg daily or less [4]. This is despite a less than 50% achievement of target uric acid levels [5]. Furthermore, it has been argued that this clinical underdosing of allopurinol is largely an artifact of an old practice of attempting to limit the risk of potentially fatal allopurinol hypersensitivity reactions and SCAR. As such, therapeutic selection and dosing strategies may be modified if *a priori* identification of patients at risk for SCAR (e.g., through preemptive genotyping or already available genetic information) could be performed in certain already at-risk populations (described in Question 3).

In order to ultimately determine whether genetic test information could have some utility in allopurinol decision-making, it is necessary to unequivocally demonstrate a strong relationship between allopurinol treatment and development of SCAR. The FDA has already qualitatively recognized this risk in the allopurinol product label. We have not quantitatively described this relationship until now.

To perform this analysis, we applied a data-mining analysis method that identifies potential safety signals in the FDA Adverse Events Reporting System (AERS) database. AERS is a spontaneous reporting database that serves as the primary data source for study and identification of postapproval adverse drug events in the USA. AERS currently contains over 5 million reports of adverse drug events submitted to the FDA by the pharmaceutical industry and the public, and the FDA receives over 1300 new reports daily. AERS has over 10,000 preferred terms in use and over 4000 decoded generic drug names in use at least once. The large number and complexity of these reports necessitate the use of statistical algorithms to supplement traditional methods of detecting drug safety problems.

A data-mining analysis of AERS was performed using Empirica Signal® software and the Multi-item Gamma Poisson Shrinker data-mining algorithm [6,7], which quantifies reported drug-event associations by producing a set of values or scores that indicate varying strengths of reporting relationships between drugs and events. These scores, denoted as empirical bayes geometric mean (EBGM) values, provide a stable estimate of the relative reporting rate of an event for a particular drug relative to all other drugs and events in the database being analyzed. Multi-item Gamma Poisson Shrinker also calculates lower and upper 90% confidence limits for the EBGM values, denoted as EB05 and EB95, respectively.

We assessed the progression by year of the association of the drug allopurinol with SCAR events defined by the preferred terms erythema multiforme (EM), SJS, and TEN (Figure 1). There were a total of 80 reports with EM, 413 with

SJS and 320 with TEN in the AERS database. The adjusted observed/expected relative reporting ratio (EBGM with lower and upper 90% CI) was significantly high for allopurinol. Specifically, when considering all drugs and events in the database, the allopurinol–SCAR event combination occurred 7.44-, 28.4- and 34.8-times more frequently than statistically expected for the combination of allopurinol and EM, SJS and TEN, respectively. While the exact degree of the association between allopurinol and SCAR in all patients exposed to the drug worldwide cannot be elicited from data-mining analyses alone, these data strongly support the association between allopurinol treatment and SCAR development.

The AERS database was subsequently searched for cases of allopurinol-exposed SCAR, which was defined as SJS/TEN/EM requiring hospitalization or resulting in death. The time period of the search was 1 January 2002 to 11 January 2009. Each case reported as SJS/TEN/EM was reviewed. The diagnosis of SCAR was defined as follows: definite or probable cases were those having dermatologist-diagnosed SJS/TEN/EM, meeting RegiSCAR criteria, or having biopsy confirmation of SJS/TEN/EM; possible cases were those reported as SJS/TEN/EM but lacking supportive data. Three investigators (Padmaja Mummaneni, Jenna Lyndly and Lois La Grenade) reviewed all reports. We identified 65 unduplicated US cases and 153 unduplicated foreign cases, all of which (total = 218 cases) were included in the cases series (Table 1). Of these, we identified two predominant subpopulations in which allopurinol-induced SCAR was reported: 32 cases reporting a comorbid condition of cancer and 61 cases reporting comorbid renal impairment (ranging from abnormal renal function test to renal failure and transplant). Five of the cases reported both a comorbid condition of cancer and renal impairment and are included in both case series.

Question 2. What is the strength of the association between *HLA* variants & allopurinol-induced SCAR?

As early as 1989, a genetic predisposition to allopurinol-associated skin eruptions was suggested in southern Chinese patients based on positive association of *HLA-B17/BW58* to the adverse event [8] with subsequent data published over the next two decades (Table 2). This report was confirmed in 2005 in a study where 823 SNPs (including 197 SNPs in the MHC region and 626 SNPs in immune-related genes and in drug-metabolizing enzymes) were screened

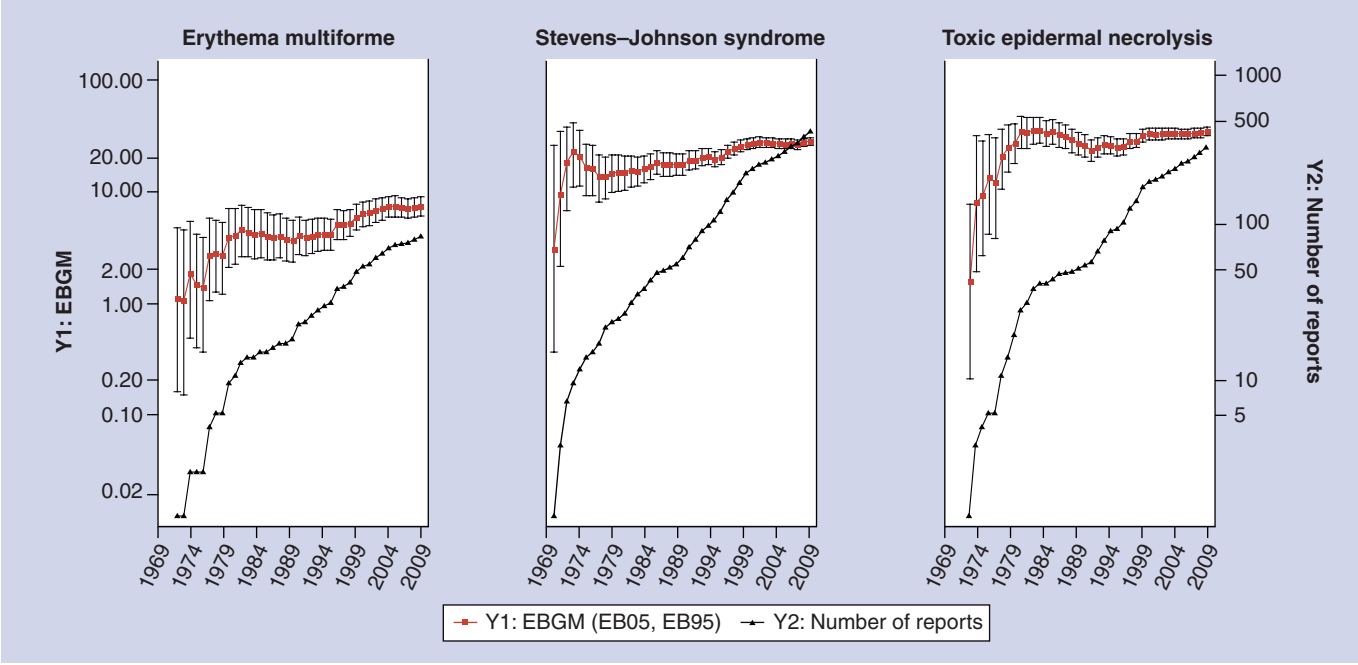

Figure 1. Temporal saftey signals for allopurinol-associated erythema multiforme, Stevens–Johnson syndrome and toxic epidermal necrolysis. The x-axis represents the year of the report labeled pentannually. The Y1-axis represents the EBGM (EB05, EB95) values and the Y2-axis the number of reports. The EGBM represents an estimate of the relative reporting ratio for allopurinol and Stevens–Johnson syndrome, toxic epidermal necrolysis or erythema multiforme compared to all other drugs and these adverse events. EB05: Lower limit of 90% confidence interval for EBGM; EB95: Upper limit of 90% confidence interval for EBGM; EBGM: Empirical Bayes geometric mean.

Table 1. Characteristics of all cases and of two subpopulations of allopurinol-associated severe cutaneous adverse reactions reported to the US FDA†.

Allopurinol-associated SCAR cases	All cases (n = 218)	Cases reporting pre-existing cancer/chemotherapy (n = 32)	Cases reporting history of renal impairment (n = 61)
Diagnosis‡	EM (19), EM/SJS (3) SJS (111), SJS/TEN (9), TEN (76)	EM (3), SJS (8), SJS/TEN (1), TEN (20)	EM (5), SJS (30), SJS/TEN (1), TEN (25)
Gender	Female (102), male (109), unknown (7)	Female (16), male (15), unknown (1)	Female (31), male (28), unknown (2)
Age in years	Median: 69; average: 67; range: 9–94; unknown (36)	Median: 64; average: 63; range: 9–86; unknown (2)	Median: 69; average: 65; range: 38–90; unknown (3)
Indications for use	Blood uric acid increased (80)‡, cardiomyopathy (1), CLL (1), CRI (1), gout (58), gouty arthritis (3), gouty nephropathy (1), hyperurikalemia (1), ill-defined disorder (5), NR (64), pain (1), prophylaxis (1), tumor lysis prophylaxis (1)	CLL (1), gout (3), hyperuricemia (8), ill-defined disorder (1), prophylaxis (1), tumor lysis prophylaxis (1), uric acid level increased (1), unknown (16)	Cardiomyopathy (1), chronic renal insufficiency (1), gout (16), gouty nephropathy (1), hyperuricemia (29), hyperurikalemia (1), unknown (12)
Peak daily dose (mg)	Median: 300; average: 225; range: 100–600; unknown (117)	Median: 200; average: 200; range: 100–300; unknown (18)	Median: 300; average: 233; range: 100–600; unknown (20)
Primary coded serious outcome (non-overlapping)	Death (79), hospitalized (103), life threatening (36)	Death (13), hospitalized (13), life threatening (6)	Death (29), hospitalization (24), life threatening (8)
Onset in days since start of allopurinol treatment	Median: 24; average: 85; range: 2–unknown; unknown (61)	Median: 35; average: 271; range: 4–3650; unknown (11)	Median: 22; average: 55; range: 2–196; unknown (7)
Cancer diagnosis	N/A	AML (4), breast cancer (4), CLL (4), B-cell lymphoma (3), multiple myeloma (3), hepatic cancer (2), non-Hodgkin's lymphoma (2), Prostate cancer (2), acute leukemia (1), ALL (1), chemotherapy (1), CML (1), leukemia (1), lymphoblastic leukemia (1), lymphoma (1), plasmacytoma (1)	N/A
Renal diagnosis (decreasing frequency)	N/A	N/A	Abnormal renal function test (1) chronic kidney disease (2), chronic renal failure (16), chronic renal insufficiency (6), cryoglobulinemic nephritis (1), decreased renal function (1), diabetic nephropathy (1), diabetic renal disease (1), glomerulonephritis proliferative chronic (1), IGA nephropathy (1), impaired renal function (1), kidney impairment (1), nephrectomy (2), renal carcinoma (2), renal failure (12), renal insufficiency (8), renal transplant (2), urate nephropathy (2)
Country	USA (63), Japan (45), Germany (30), France (24), Italy (20), Thailand (5), Canada (3), Republic of Korea (3), Spain (3), Sweden (3), Switzerland (3), UK (3), Israel (2), Australia (1), Denmark (1), Greece (1), Hong Kong (1), Indonesia (1), Ireland (1), Malaysia (1), Philippines (1), Portugal (1), Singapore (1), Taiwan (1)	USA (8), Japan (7), Germany (5), Italy (3), France (2), Sweden (2), Canada (1), UK (1), Greece (1), Switzerland (1), unknown (1)	Japan (16), USA (15), France (8), Germany (8), Italy (5), South Korea (2), Spain (2), Switzerland (2), Canada (1), Portugal (1), Taiwan (1)

†1 January 2001–31 October 2009.
‡Blood uric acid increased (1), elevated uric acid level (1), hyperuricemia (1), hyperuricemia (75), increased uric acid (1) and uric acid level increased (1).
ALL: Acute lymphoblastic leukemia; AML: Acute myeloid leukemia; CLL: Chronic lymphocytic leukemia; CML: Chronic myelogenous leukemia; CRI: Chronic renal insufficiency; EM: Erythema multiforme; IGA: Immunoglobulin A; N/A: Not applicable; NR: Not reported; SCAR: Severe cutaneous adverse reactions; SJS: Stevens–Johnson syndrome; TEN: Toxic epidermal necrolysis.

and the strongest association found was that of *HLA-B*5801* with allopurinol-induced SJS/TEN/hypersensitivity syndrome (HSS) in Han Chinese patients [9]. All 51 patients with allopurinol-associated SJS/TEN/HSS were carriers of *HLA-B*5801*. Even though all the SCAR patients were carriers of *HLA-B*5801*, 15% of the allopurinol-tolerant controls were also positive for the allele. Almost identical results were reported in Thai patients where all 27 cases were carriers of the *HLA-B*5801* allele and 13% of tolerant controls were positive for the allele [10]. A similar but more modest association was observed in a European study where 15 out of 27 (55%) Caucasians with allopurinol-induced SJS/TEN carried the *HLA-B*5801* allele, whereas 28 out of 1822 (1.5%) of the controls were positive for the allele [11]. In a study conducted in Japan, 40% (four out of ten cases) of the cases were found to be carriers of the *HLA-B*5801* allele, whereas, only three out of 493 (0.61%) healthy controls were *HLA-B*5801* positive [12]. Another small report from Japan supported the association with the *HLA* allele where three cases were carriers of the *HLA-B*5801* allele [13]. Finally, a recent study of Korean subjects with allopurinol-associated SCAR found that four out of five (80%) of SJS/TEN cases were carriers of the *HLA-B*5801* allele, while only six out of 57 (11%) of allopurinol-tolerant and 59 out of 485 (12%) healthy controls were carriers of the *HLA-B*5801* allele [14]. Association studies to date as well as our pooled assessment are summarized in Table 2.

The true relative risk for *HLA-B*5801* is difficult to estimate from the published data. We performed a pooled analysis of published studies, which suggests the odds ratio of allopurinol-associated SCAR in *HLA-B*5801* carriers is approximately 73 (95% CI: 32–164) for studies using healthy controls and 165 (95% CI: 23–1174) for studies using allopurinol-tolerant controls (odds ratios calculated using Mantel–Haenszel method, random effects model). In both analyses, no evidence for significant heterogeneity of the estimates was observed across studies (I^2 = 16% for healthy control studies; I^2 = 38% for healthy control studies) [15], and publication bias does not appear to be present based on inspection of funnel plots. The variability in the relative odds across studies may be related to the ethnic diversity of patients included in the various studies although a similar degree of heterogeneity is observed when including only studies of Asian populations (data not shown). Otherwise, differences may be driven by study methodology and sample sizes, heterogeneity in case or control definitions, assay methods, or lack of events in some of the genotype groups. Risk estimates from studies with drug-exposed controls, which tended to be larger, may be particularly relevant considering that some population controls could eventually become cases, thereby biasing risk estimates toward the null. Nonetheless, the confidence intervals reported in each study suggest that the odds ratios for SCAR in *HLA-B*5801* carriers in general at least ten. While heterogeneity in the strength of the association exists, the association between *HLA-B*5801*

Table 2. Individual and pooled assessment of *HLA-B*5801* associations with allopurinol-induced severe cutaneous adverse reactions.

Population	*HLA-B*5801* prevalence in allopurinol-SCAR cases and controls	Odds ratio (95% CI)	Sensitivity (%)/ specificity (%)	p-value	Ref.
Han Chinese	Cases: 51/51 (100%)				[9]
	Tolerant controls: 20/135 (15%)	580 (34–9781)†	100/85	4.7×10^{-24}†	
	Healthy controls: 19/93 (20%)	393 (23–6625)‡	100/80	8.1×10^{-18}‡	
European	Cases: 15/27 (55%)				[11]
	Healthy controls: 28/1822 (1.5%)	80 (34–87)	56/99	$<10^{-6}$	
Japanese	Cases: 4/10 (40%)				[12]
	Healthy controls§: 6/493 (0.1%)	54 (10–311)	40/99	<0.0001	
Thai	Cases: 27/27 (100%)				[10]
	Tolerant controls: 7/54 (13%)	348 (19–6337)	100/87	1.6×10^{-13}	
Korean	Cases: 4/5 (80%)				[14]
	Tolerant controls: 6/57 (11%)	34 (3–947)†	80/90	1.6×10^{-2}†	
	Healthy controls: 59/485 (12%)	29 (3–703)‡	80/88	1.0×10^{-2}‡	
Pooled analysis	Cases: 101/120 (84%)				
	All controls: 145/3139 (4.6%)	90 (36–231)	84/95	1.8×10^{-102}	

†*Compared with tolerant controls.*
‡*Compared with healthy controls.*
§*Assumes alleles come from heterozygous individuals in the original publication.*
SCAR: Severe cutaneous adverse reaction.

positivity and likelihood for allopurinol-associated SCAR is strong and highly significant.

In addition to the robust magnitude of the observed association between *HLA* variation and allopurinol-induced SCAR, some have hypothesized a mechanistic link between *HLA* variations and immunological mediation of drug-induced SCAR [16]. Furthermore, a number of pharmacogenomic evaluations of drug-induced adverse events including phenotypes related to liver injury, osteonecrosis, myopathy, skin reactions and others have been conducted. Of particular relevance, the clear majority of adverse event genome-wide association studies have implicated variants in the *HLA* loci as the strongest links to many of these adverse events, most notably in cutaneous adverse events for various drug classes [17]. These findings generally implicate immune genes as correlates of adverse event risk and add further strength to the specific findings implicating *HLA* variation and allopurinol-induced SCAR.

Question 3. What nongenetic variables are associated with risk for allopurinol-induced SCAR?

The exact 'at-risk' profile of patients predisposed to allopurinol-induced SCAR has not been robustly identified. However, several risk factors for increased risk have been described. Allopurinol hypersensitivity has been attributable, at least in part, to accumulation of the renally eliminated oxypurinol metabolite [5]. While the exact threshold for oxypurinol levels and excess risk is not well established and is controversial [18], renal impairment has been empirically associated with increased risk for SCAR in patients taking allopurinol [9]. In some reports, patients with renal dysfunction treated with allopurinol are three- to four-times more likely to experience hypersensitivity reactions than those with normal renal function [19]. Another estimate suggests that renal insufficiency may be the most robust nongenetic variable of allopurinol hypersensitivity carrying an odd ratio of 4.7 (95% CI: 2.3–9.3; $p < 0.0001$) [9]. Renal dysfunction is described as a risk factor for allopurinol-induced adverse events in the drug package insert, and as such, dose adjustment for patients with renal impairment is typically recommended in dosing guidelines.

Risk of hypersensitivity has been described to be increased in patients receiving allopurinol and various concomitant therapies. For example, while maculopapular rash is estimated to occur in approximately 2% of allopurinol-treated patients, this number increases to 20% in patients taking allopurinol with ampicillin or amoxicillin [20]. Hypersensitivity in patients with renal dysfunction receiving concomitant thiazide diuretics and allopurinol has also been described, and is noted in the warnings section of the allopurinol product label. The exact mechanism of the increased risk of cutaneous reactions upon concomitant treatment with allopurinol and these drugs is not known.

While the exact constellation of nongenetic risk factors that confers the greatest risk of allopurinol-induced hypersensitivity is unknown, the following should generally be considered in assessing the potential risk (i.e., relative to benefit) of allopurinol treatment for a given patient: recent initiation of allopurinol, chronic kidney disease, concomitant thiazide or penicillin/cephalosporin use, high allopurinol dose relative to renal function and treatment of asymptomatic hyperuricemia [20]. In addition, our case assessments (Table 1) support the contention that risk of SCAR may be elevated in patients being treated with allopurinol in cancer settings, where it is used to mitigate metabolic complications of cancer treatment (e.g., tumor lysis syndrome). Other hypothesized risk factors that require further study include: history of allergic reactions to other medications in general, history of allergic reactions to other medications know to be associated with *HLA* gene region variants (e.g., penicillins, abacavir, antiepileptic drugs and NSAIDs) and family history of allergy to allopurinol or other drugs.

Question 4. What are the clinical courses of action for patients who are genetically at risk for allopurinol-induced SCAR?

In order for genetic (or other) information to be meaningful to clinical decision-making, the test result must be 'actionable'. That is, clinicians are only likely to use *HLA* genotype information if the test results can be tied to alternative doses, alternative treatments and/or more frequent monitoring. It is likely to be a clinician-specific decision of whether or not to test for *HLA* genotypes based on whether the patient exhibits any of the putative risk factors discussed in Question 3, or whether they have a pretreatment assessment that high doses of allopurinol are likely to be needed for a given patient (e.g., very high uric acid concentrations or frequent/severe gout flares). Notwithstanding, several courses of action based on genotype results are possible.

Because of the relatively high specificity of *HLA-B*5801* typing with respect to allopurinol hypersensitivity (TABLE 2), a positive genotype test may give a clinician cause for pause when prescribing allopurinol. Patients with a negative test result may be treated per professional guidelines. Patients with a positive test may be good candidates for alternative treatments. Irrespective of testing, all patients should be afforded specific counseling on the signs and symptoms of hypersensitivity, and counseled to discontinue treatment immediately and contact their prescriber if any of these occur. It is still controversial as to whether allopurinol SCAR is a dose-dependent toxicity; therefore, if a decision is made to use the 'start low, go slow' paradigm in *HLA-B*5801*-positive patients, extreme caution and careful monitoring is prudent.

Conclusion

Allopurinol is a commonly prescribed drug for the management of gout and hyperuricemia. While generally well tolerated, allopurinol is associated with rare, potentially life-threatening cutaneous reactions which are described in the FDA-approved drug label. In this paper, we describe the community exposure to allopurinol using drug-use data. Additionally, we quantified the drug–adverse event risk using a validated data-mining algorithm of the FDA AERS database. Genetic associations between *HLA* variants and allopurinol-induced SCAR have been described. We performed pooled analyses of the published literature to elucidate the expected risk of SCAR associated with *HLA* gene variation. We found the associations between *HLA-B*5801* to be strong, reproducible and consistent with other observations from genome-wide association studies of other adverse events implicating *HLA* genes. This suggests that allopurinol may need to be avoided in patients who are known carriers of the *HLA-B*5801* may need to be closely monitored. We applied a question-based framework to highlight considerations in assessing the utility of *HLA* genotype information in treatment decisions. Our approach may be particularly relevant for safety pharmacogenetics given the infeasibility of conducting prospective, randomized trials for rarer safety events.

Future perspective

There will continue to be significant interest in the selective application of pharmacogenomics to patient care. In addition to the questions raised above, a fifth question for consideration by some decision-makers might include: what are the cost considerations of genetic testing? Though quantifying the economics of allopurinol pharmacogenetic testing is beyond the scope of our article, there has been an interesting paradigm shift worth mentioning that is reframing how some individuals think about pharmacoeconomic assessment of pharmacogenomics. In early pharmacogenomic models, the cost of testing was a major consideration in determining whether there was added value in ordering a pharmacogenomic test in clinical practice. Now, however, some suggest that the significant investment in information technology and the electronic medical record allow a multiplex genetic test (i.e., one which covers many relevant pharmacogenes) to be linked to a patient's medical record for their lifetime, negating the need for drug-specific tests to be performed in one-off clinical contexts. This model will make pharmacogenomic test costs negligible and change the question from 'should I order a test?' to 'how can I use this patient's available genetic information?' In fact, this 'preemptive' genotyping model is the major presumption of groups currently developing pharmacogenomic guidelines to aid incorporation of pharmacogenomics into routine clinical practice decisions [21].

Cost considerations aside, there are other ways one can think about the usefulness of a pharmacogenetic biomarker. For a severe adverse event with high-case fatality, a marker with a high negative predictive value would be desirable to allow patients not at risk for the adverse event to receive treatment. This is particularly relevant if the treatment is expected to effectively treat a morbid condition or prevent a mortal event. In the allopurinol context, false positives (in which a decision may be erroneously made not to treat with allopurinol) might be acceptable considering the availability of alternative therapies in the setting of gout. The clinical performance characteristics of *HLA-B*5801* genotyping cannot be determined using the existing case–control data and lack of clearly defined incidence rates for SJS/TEN in patients receiving allopurinol. However, assuming a SJS/TEN incidence of approximately one in 10,000 per year, the positive and negative predictive values are estimated to be <1% and 99.9%, respectively, as expected for a common genetic marker to predict a rare adverse event. The number required to test positive in order to prevent one adverse event will be influenced by the true incidence of the adverse event and the prevalence of the genetic marker in the

population tested. As such, it may be most effective to focus testing on those patient subgroups that are at higher risk because of other factors (see Question 3 above). Metrics such as 'number needed to test' may be less relevant in health systems where preemptive genotyping coupled with an electronic clinical decision support system is available. As pharmacogenetic information becomes more readily available to clinicians and patients, new dimensions of utility are likely to shape the personalized medicine public health dialog in the next 5–10 years.

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Executive summary

Background

- Optimal use of pharmacogenetics remains a priority of the US FDA.
- We previously developed a framework for assessing the potential utility of pharmacogenetic information, and here we apply the framework to the association between *HLA* gene variation and allopurinol-induced severe cutaneous adverse reactions (SCAR).

Question 1. What is the medical need for the genetic test?

- One must, in part, consider the size of the potential population exposed to the drug of interest and the risk of the adverse event in exposed populations to determine whether there is a potential medical need for a pharmacogenetic test to guide treatment decisions.
- Drug-use data compiled from FDA databases suggest substantial allopurinol exposure.
- Allopurinol may be routinely underdosed due to fear of SCAR. We assessed allopurinol cutaneous safety signals using the FDA Adverse Events Reporting System database and in addition found significant reporting relationships between allopurinol use and erythema multiforme, Stevens–Johnson syndrome and toxic epidermal necrolysis over time.
- The subpopulations of patients who experienced SCAR included those with renal dysfunction and patients with cancer.

Question 2. What is the strength of the association between* HLA *variants & allopurinol-induced SCAR?

- Several published reports implicate *HLA-B*5801* and allopurinol-associated SCAR.
- A preponderance of the data comes from Asian patients.
- Our pooled analysis of published studies suggests the odds ratio of allopurinol-associated SCAR in *HLA-B*5801* carriers is approximately 73 (95% CI: 32–164) for studies using healthy controls and 165 (95% CI: 23–1174) for studies using carbamazepine-tolerant controls.
- Despite heterogeneity in the studies, the confidence intervals reported in each study suggest that the odds ratios for SCAR in *HLA-B*5801* carriers are generally at least 10.

Question 3. What nongenetic variables are associated with risk for allopurinol-induced SCAR?

- Renal dysfunction is a risk factor for allopurinol-induced adverse events, and dose adjustment for patients with renal impairment is typically recommended in dosing guidelines.
- Risk of hypersensitivity has been described to be increased in patients receiving allopurinol and various concomitant therapies such as ampicillin or amoxicillin.
- Hypersensitivity in patients with renal dysfunction receiving concomitant thiazide diuretics and allopurinol has also been described.
- The following may be considered in determining the potential risk (relative to benefit) of allopurinol treatment for a given patient: recent initiation of allopurinol, chronic kidney disease, concomitant thiazide or penicillin/cephalosporin use, high allopurinol dose relative to renal function, treatment of asymptomatic hyperuricemia and use in cancer settings.
- Risk factors that need further study include: history of allergic reactions to other medications in general, history of allergic reactions to other medications know to be associated with *HLA* gene region variants (e.g., penicillins, abacavir, antiepileptic drugs and NSAIDs), and a family history of allergy to allopurinol or other drugs.

Question 4. What are the clinical courses of action for patients who are genetically at risk for allopurinol-induced SCAR?

- It is likely to be a clinician-specific decision of whether or not to test for *HLA* genotypes.
- Once test information is available, several courses of action are conceivable including: treat as usual in test-negative patients, consider alternative treatments in test-positive patients. In addition all patients should be afforded specific counseling on the signs and symptoms of hypersensitivity, and counseled to discontinue treatment immediately and contact their prescriber if any of these occur.

Conclusion

- While generally well tolerated, allopurinol is associated with rare, potentially life-threatening cutaneous reactions that are described in the FDA-approved drug label.
- We performed pooled analyses of the published literature to elucidate the expected risk of SCAR associated with *HLA* gene variation and associations with *HLA-B*5801* to be strong, reproducible and consistent with other observations from genome-wide association studies of other adverse events implicating *HLA* genes.

Future perspective

- There will continue to be significant interest in the selective application of pharmacogenomics to patient care.
- The newly recognized shift to 'preemptive' genotyping may make metrics such as 'number needed to test' less relevant in the pharmacoeconomic evaluation of pharmacogenetic tests.
- As pharmacogenetic information becomes more readily available to clinicians and patients, new dimensions of utility are likely to shape the personalized medicine public health dialog in the next 5–10 years.

Disclosure

The views expressed are those of the authors and do not necessarily reflect US FDA policy. No official endorsement is intended nor should be inferred.

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References

Papers of special note have been highlighted as:
- ▪ of interest
- ▪▪ of considerable interest

1 Zineh I, Lesko LJ. Pharmacogenetics in medicine: barriers, critical factors and a framework for dialogue. *Per. Med.* 6, 359–361 (2009).

▪▪ **Highlights the 'pharmacogenetic pyramid' as a framework for assessing potential utility of pharmacogenomic information. The question-based framework is the one used in the current manuscript to assess the potential value of allopurinol pharmacogenetics.**

2 Jordan KM, Cameron JS, Snaith M *et al.* British Society for Rheumatology and British Health Professionals in Rheumatology Standards, Guidelines and Audit Working Group (SGAWG). British Society for Rheumatology and British Health Professionals in Rheumatology guideline for the management of gout. *Rheumatology (Oxford)*. 46(8), 1372–1374 (2007).

3 Zhang W, Doherty M, Bardin T *et al.* EULAR Standing Committee for International Clinical Studies including Therapeutics. EULAR evidence based recommendations for gout. Part II: management. Report of a task force of the EULAR Standing Committee for International Clinical Studies Including Therapeutics (ESCISIT) *Ann. Rheum. Dis.* 65(10), 1312–1324 (2006).

4 Sarawate CA, Brewer KK, Yang W *et al.* Gout medication treatment patterns and adherence to standards of care from a managed care perspective. *Mayo. Clin. Proc.* 81(7), 925–934 (2006).

5 Chohan S, Becker MA. Update on emerging urate-lowering therapies. *Curr. Opin. Rheumatol.* 21(2), 143–149 (2009).

6 DuMouchel W, Pregibon D. Empirical Bayes screening for multi-item associations. In: *KDD '01: Proceedings of the Seventh ACM SIGKDD International Conference on Knowledge Discovery and Data Mining*. ACM, New York, NY, USA, 67–76 (2001).

7 Szarfman A, Machado SG, O'Neill RT. Use of screening algorithms and computer systems to efficiently signal higher-than-expected combinations of drugs and events in the US FDA's spontaneous reports database. *Drug Saf.* 25, 381–392 (2002).

▪ **Provides background on the adverse event data mining methodology alluded to in this article.**

8 Chan SH, Tan T. *HLA* and allopurinol drug eruption. *Dermatologica* 179(1), 32–33 (1989).

9 Hung SI, Chung WH, Liou LB *et al.* *HLA-B*5801* allele as a genetic marker for severe cutaneous adverse reactions caused by allopurinol. *Proc. Natl Acad. Sci. USA* 102(11), 4134–4139 (2005). Erratum in: *Proc. Natl Acad. Sci. USA* 102(17), 6237 (2005).

10 Tassaneeyakul W, Jantararoungtong T, Chen P *et al.* Strong association between *HLA-B*5801* and allopurinol-induced Stevens–Johnson syndrome and toxic epidermal necrolysis in a Thai population. *Pharmacogenet. Genomics* 19(9), 704–709 (2009).

11 Lonjou C, Borot N, Sekula P *et al.* RegiSCAR study group. A European study of *HLA*-B in Stevens–Johnson syndrome and toxic epidermal necrolysis related to five high-risk drugs. *Pharmacogenet. Genomics* 18(2), 99–107 (2008).

12 Kaniwa N, Saito Y, Aihara M *et al.* JSAR research group. *HLA*-B locus in Japanese patients with anti-epileptics and allopurinol-related Stevens–Johnson syndrome and toxic epidermal necrolysis. *Pharmacogenomics* 9(11), 1617–1622 (2008).

13 Dainichi T, Uchi H, Moroi Y, Furue M. Stevens–Johnson syndrome, drug-induced hypersensitivity syndrome and toxic epidermal necrolysis caused by allopurinol in patients with a common *HLA* allele: what causes the diversity? *Dermatology* 215(1), 86–88 (2007).

14 Kang HR, Jee YK, Kim YS *et al.* Positive and negative associations of *HLA* class I alleles with allopurinol-induced SCARs in Koreans. *Pharmacogenet. Genomics* 21(5), 303–307 (2011).

15 Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ* 327(7414), 557–560 (2003).

16 Chung WH, Hung SI. Genetic markers and danger signals in Stevens–Johnson syndrome and toxic epidermal necrolysis. *Allergol. Int.* 59(4), 325–332 (2010).

17 Daly AK. Pharmacogenetics and human genetic polymorphisms. *Biochem. J.* 429(3), 435–449 (2010).

18 Puig JG, Casas EA, Ramos TH, Michán AA, Mateos FA. Plasma oxypurinol concentration in a patient with allopurinol hypersensitivity. *J. Rheumatol.* 16(6), 842–844 (1989).

19 Khanna D, Fuldeore MJ, Meissner BL *et al.* The incidence of allopurinol hypersensitivity syndrome: a population perspective. Presented at: *The Annual American College of Rheumatology Scientific Meeting (ACR/ARHP)*. Poster Session C S672, San Francisco, CA, USA, 23–28 October 2008.

20 Chao J, Terkeltaub R. A critical reappraisal of allopurinol dosing, safety, and efficacy for hyperuricemia in gout. *Curr. Rheumatol. Rep.* 11(2), 135–140 (2009).

▪ **Assesses the potential root causes of suboptimal allopurinol dosing. The authors assess the relationship between allopurinol hypersensitivity and renal dysfunction and provide a review of allopurinol dosing guidelines, including for patients with chronic kidney disease.**

21 Relling MV, Klein TE. CPIC: Clinical Pharmacogenetics Implementation Consortium of the Pharmacogenomics Research Network. *Clin. Pharmacol. Ther.* 89(3), 464–467 (2011).

▪ **Describes one of the newer pharmacogenomics evidence assessment initiatives. Specifically, Clinical Pharmacogenetics Implementation Consortium is a guideline-writing group whose evidence assessment and recommendation model assumes a 'preemptive' genotyping strategy as articulated in this article.**