Use of HLA-B*58:01 genotyping to prevent allopurinol induced severe cutaneous adverse reactions in Taiwan: national prospective cohort study

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ABSTRACT

OBJECTIVE

To evaluate the use of prospective screening for the HLA-B*58:01 allele to identify Taiwanese individuals at risk of severe cutaneous adverse reactions (SCARs) induced by allopurinol treatment.

DESIGN

National prospective cohort study.

SETTING

15 medical centres in different regions of Taiwan, from July 2009 to August 2014.

PARTICIPANTS

2926 people who had an indication for allopurinol treatment but had not taken allopurinol previously. Participants were excluded if they had undergone a bone marrow transplant, were not of Han Chinese descent, and had a history of allopurinol induced hypersensitivity. DNA purified from 2910 participants' peripheral blood was used to assess the presence of HLA-B*58:01.

MAIN OUTCOME MEASURES

Incidence of allopurinol induced SCARs with and without screening.

RESULTS

Participants who tested positive for HLA-B*58:01 (19.6%, n=571) were advised to avoid allopurinol, and were referred to an alternate drug treatment or advised to continue with their prestudy treatment. Participants who tested negative (80.4%, n=2339) were given allopurinol. Participants were interviewed once a week for two months to monitor symptoms. The historical incidence of allopurinol induced SCARs, estimated by the National Health Insurance research database of Taiwan, was used for comparison. Mild, transient rash without blisters developed in 97 (3%) participants during follow-up. None of the participants was admitted to hospital owing to adverse drug reactions. SCARs did not develop in any of the participants receiving allopurinol who screened negative for HLA-B*58:01. By contrast, seven cases of SCARs were expected, based on the estimated historical incidence of allopurinol induced SCARs nationwide (0.30% per year, 95% confidence interval 0.28% to 0.31%; P=0.0026; two side one sample binomial test).

CONCLUSIONS

Prospective screening of the HLA-B*58:01 allele, coupled with an alternative drug treatment for carriers, significantly decreased the incidence of allopurinol induced SCARs in Taiwanese medical centres.

WHAT IS ALREADY KNOWN ON THIS TOPIC

Allopurinol, a first line prescription drug treatment for gout and hyperuricaemia, is one of the most common causes of severe cutaneous adverse reactions (SCARs) in many countries

There is a strong association between the HLA-B*58:01 allele and allopurinol induced SCARs in people of Han Chinese, Thai, Japanese, Korean, European, and Portuguese descent

Prospective screening for HLA-B*58:01 before allopurinol treatment in patients with an indication for allopurinol treatment could help reduce the incidence of allopurinol induced SCARs

WHAT THIS STUDY ADDS

Using information from the National Health Insurance research database of Taiwan, a historical incidence of seven cases of SCARs was predicted among participants receiving allopurinol treatment in a prospective study of adequate sample size

By contrast, in the present study, none of the HLA-B*58:01 negative participants who received allopurinol treatment developed SCARs during study follow-up

This pharmacogenomics approach could provide a strong basis for implementation of personalised medicine

Introduction

The development of a reliable pharmacogenomic approach to prevent adverse reactions with severe complications is a major goal of personalised medicine.[1-3] Severe cutaneous adverse reactions (SCARs) constitute a set of life threatening conditions that include drug rash with eosinophilia and systemic symptoms, Stevens-Johnson syndrome, and toxic epidermal necrolysis,[4] with the lethality rate of toxic epidermal necrolysis at up to 35%. SCARs are often caused by drugs but may not be accurately predicted based on the pharmacological action of a particular drug.[5] SCARs are associated

with chemotoxic and T cell mediated inflammatory injuries, and can be characterised by a severe idiosyncratic reaction in skin, blistering exanthema of macular papules, or mucosal involvement.[6]

Allopurinol, a first line prescription drug for gout and hyperuricaemia,[7-10] is one of the most common causes of SCARs in Asia and Europe.[11-13] Throughout 2012, the literature reported about 1000 people who had allopurinol induced SCARs; these patients represented multiple ethnic origins and geographical regions.[12] Although allopurinol has SCAR related risks and other drug treatments for gout are available, allopurinol is still a common treatment for gout and hyperuricaemia owing to its relative low cost, efficacy, and convenience.

We have reported previously that allopurinol induced SCARs correlate strongly with the allele human leukocyte antigen (HLA)-B*58:01 in Han Chinese populations.[14] This finding has been confirmed in Han Chinese people from Hong Kong and mainland China, and in Japanese, Korean, Thai, and other Asian populations as well as European populations.[15-21] Among people of Han Chinese descent, allopurinol induced SCARs almost never occur in non-carriers of HLA-B*58:01, strongly suggesting that this allele is involved directly in the pathogenesis of SCARs. In addition, HLA-B*58:01 can present the allopurinol metabolite, oxypurinol, directly to cytotoxic T cells without antigen processing.[22-24] More importantly, T cell mediated cytotoxicity related to allopurinol or oxypurinol is restricted to carriers of HLA-B*58:01.[23 24]

Based on our previous findings,[14] Han Chinese people who carry HLA-B*58:01 have a much higher risk of developing allopurinol induced SCARs than those who do not carry the allele (odds ratio 580.3; 95% confidence interval 34.4 to 9780.9; P<0.001). Therefore, if this allele was to be used as a marker to predict allopurinol induced SCARs, the test would have high sensitivity (100.0%) and specificity (85.2%).[14] Based on a predicted incidence of allopurinol induced SCARs of 0.30% per year (95% confidence interval 0.28% to 0.31%), HLA-B*58:01 would have a negative predictive value of 100.0% and a positive predictive value of 2.0%. Thus, the 100% negative predictive value could warrant the use of HLA-B*58:01 genotyping to prevent allopurinol induced SCARs in routine clinical practice. We therefore sought to determine whether prospective screening via HLA-B*58:01 genotyping before allopurinol treatment could reduce the incidence of allopurinol induced SCARs.

Methods

Study design

Owing to the tight association between HLA-B*58:01 and life threatening SCARs induced by allopurinol, this study was approved by our institutional review board as a non-randomised study, using historical incidence as a control. We recruited patients from 15 participating hospitals throughout Taiwan (see author affiliations and web appendix). There were nine points of interaction with patients who did not have the HLA-B*58:01 allele and 10 points of interaction with HLA-B*58:01 carriers: the initial screening visit, a second clinic visit for HLA-B*58:01 carriers, and weekly telephone interviews for both groups during the two month follow-up. Recruited patients were aged between 6 months and 99 years, and had not previously taken allopurinol within three months. In accordance with clinical indications at the time of screening, these patients would have received allopurinol and thus were invited to participate in the study. The efficacy of all treatments to reduce levels of uric acid was evaluated on the basis of the guideline for gout management.[8-10]

We excluded patients who had undergone a bone marrow transplant, were not of Han Chinese descent, and had a history of allopurinol induced hypersensitivity. Han Chinese descent was confirmed via a multiple choice questionnaire that asked patients to report the ethnic origin of both parents and grandparents.

We prescribed and dispensed allopurinol to all participants at the initial screen, but we asked that each person defer taking allopurinol until the HLA-B*58:01 genotyping results were finalised. Blood samples were collected and transferred to our central laboratory for HLA-B*58:01 genotyping. We reported the genotyping results to the participating physicians within three days.

Patients who tested positive for HLA-B*58:01 were asked to return to their respective hospitals within three days. We then explained their risk of allopurinol induced SCARs and recommended that they take alternative medicine. Those who tested negative for HLA B*58:01 (and who also were counselled about SCARs risk) were started on allopurinol treatment. In our previous large scale retrospective study,[14] all patients developed SCARs during the study period within two months of starting allopurinol treatment, which was in agreement with what has been reported consistently in the literature.[25] We therefore interviewed all participants by telephone during the two month period following initial screening (for HLA-B*58:01 negative patients) or after the second clinic visit (for HLA-B*58:01 positive patients) to monitor for symptoms of adverse drug reactions, including SCARs. If early symptoms of SCARs developed, a participant was asked to return to the clinic immediately for dermatological evaluation. We monitored all patients throughout the study's duration, apart from those who had a protocol violation or were lost during follow-up.

The study was performed in accordance with Good Clinical Practice Standards and the provisions of the Declaration of Helsinki. The research ethics committee at Academia Sinica in Taipei and the institutional review board at each participating clinic approved the study. We obtained written informed consent from all participants or from parents or guardians for participants aged 21 years or younger.

Genotyping of HLA-B*58:01

Whole blood (2 mL) was collected from each participant in a Monovette tube and stored at 4-12°C, and each sample was sent to the central lab on the day obtained. We isolated genomic DNA with the QIAamp DNA purification

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system (Qiagen). The presence or absence of HLA-B*58:01 was determined by the PG5801 DNA detection kit (Pharmigene). The kits are based on a real time polymerase chain reaction with sequence specific primers for HLA-B*58:01. To confirm the genotyping results, the first 900 samples were also examined in parallel with a reverse line blot using an HLA sequence oligonucleotide (Dynal Biotech); the results were consistent in each sample.

Annual incidence

We diagnosed SCARs using code 695.1 in both ICD-9 (international classification of diseases, 9th revision) and ICD-9-CM (clinical modification), which are commonly used in studies of adverse drug reactions.[26 27] The ICD-9-CM 695.1 code covers all SCARs, including drug rash with eosinophilia and systemic symptoms, Stevens-Johnson syndrome, and toxic epidermal necrolysis. The number of participants with this code was determined from the National Health Insurance research database, as provided by the National Health Insurance administration of Taiwan.

The National Health Insurance research database is reliable and applies to nationwide studies in Taiwan,[28-30] and was established by the Taiwanese government when the National Health Insurance system was launched in 1995. The database is a single payer health insurance plan managed by the Taiwanese government, and provides healthcare for nearly all the Taiwanese population (enrolment was 99.5% in 2008). More than 92% of Taiwanese healthcare facilities have been contracted by the National Health Insurance system. Data obtained from the National Health Insurance research database are therefore comprehensive.

We estimated the annual incidence of allopurinol induced SCARs in Taiwan as the annual number of SCARs cases caused by allopurinol divided by the annual number of new allopurinol users. In 2005, we published an article stating the potential of HLA-B*58:01 as a biomarker for preventing allopurinol-induced SCARs.[14] After this, some physicians began to genotype HLA-B region before allopurinol treatment. This measure could confound our analysis. Therefore, to obtain a suitable control group, we adopted the most recent, non-confounded data (that is, 2001-04 data) from the National Health Insurance research database.

Statistical analysis

The prevalence of the HLA-B*58:01 allele in the Han Chinese population residing in Taiwan has been calculated to be 20%.[31] Therefore, 2169 people would provide a power of 86% (using the two sided, one sample binomial test) to detect a reduction in the incidence of allopurinol induced SCARs from 0.30% per year (95% confidence interval 0.28% to 0.31%; that is, 30 cases per 10 000 new recipients) to 0.03%. We used the two sided, one sample binomial test to compare the rate of allopurinol induced SCARs in the prospective screening population with historical incidence. All P values are two tailed, and $P<0.05$ was considered to be significant.

Patient involvement

No patients were involved in setting the research question or the outcome measures, nor were they involved in the design and implementation of the study. There are no plans to involve patients in dissemination.

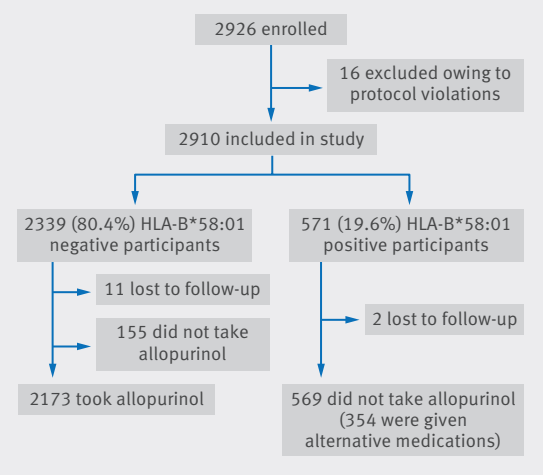
Results

Participants

From July 2009 to August 2014, we enrolled 2926 participants, of whom 2910 underwent genotyping and were included in the two month follow-up (fig). Male and female patients accounted for 83% and 17% of the total group, respectively, with mean age 54.9 years (range 14-99; table 1). Indications for allopurinol treatment included chronic tophaceous gout (35%), hyperuricaemia (24%), chronic tophaceous gout plus hyperuricaemia (16%), chronic tophaceous gout plus other conditions (7%), and other conditions (17%; table 1).

HLA-B*58:01 screening

Of the 2910 enrolled participants, 571 (20%) were identified as carrying the HLA-B*58:01 allele and were counselled not to take allopurinol; these patients were prescribed alternative drugs or counselled to continue taking their medication before the study. Of these participants, we monitored for adverse events and found that two were lost during follow-up, 354 took an alternative drug treatment, and 215 took their prestudy medication (fig). Alternative drug treatments were benzbromarone, bisoprolol fumarate, bromhexine hydrochloride, brompheniramine, colchicine, febuxostat, hydroxychloroquine, sulfasalazine, sulfonylurea, and sulfinpyrazone (web table). Of the remaining 2339 (80%) participants who did not have the HLA-B*58:01 allele, 155 did not take allopurinol and 11 were lost during follow-up. This left 2173 participants who took allopurinol and were monitored (fig).



Enrolment and outcomes. Allopurinol was prescribed and provided for all participants at the time of the screening visit, but they were asked to defer taking the drug until the results of genetic testing were available. All participants, regardless of allele status, were followed for three months, with weekly telephone interviews

Table 1 | Participant characteristics

Characteristic	Presence of HLA-B*58:01 allele: Positive (n=571)	Negative (n=2339)	P*	Total (n=2910)
Sex (No (%))				
Male	460 (80.6)	1950 (83.4)	0.11	2410 (82.8)
Female	111 (19.4)	389 (16.6)	0.11	500 (17.2)
Age (years)				
Mean (range)	54.8 (19-99)	54.9 (14-95)	0.86	54.9 (14-99)
Kidney function (No)†				
Renal insufficiency	120	444	0.27	564
Indication for allopurinol (No (%))				
Chronic tophaceous gout	204 (35.7)	820 (35.1)	0.76	1024 (35.2)
Hyperuricaemia	141 (24.7)	555 (23.7)	0.63	696 (23.9)
Chronic tophaceous gout plus hyperuricaemia	97 (17.0)	371 (15.9)	0.51	468 (16.1)
Chronic tophaceous gout plus other	43 (7.5)	173 (7.4)	0.91	216 (7.4)
Other conditions‡	86 (15.1)	420 (18.0)	0.10	506 (17.4)

*Comparison of clinical characteristics between HLA-B*58:01 positive and negative participants.
†Renal insufficiency was defined as greater than 1.3 mg/dL of serum creatinine.
‡Including urate nephropathy, prevention of recurrent nephrolithiasis, and prevention of recurrent calcium oxalate stones.

Adverse events

Of 2910 participants, 97 (3%) developed mild and transient rash and itching, but none had a combination of rash, itching, and localised blisters (table 2). Of those with rash or itching, three participants were found to carry HLA-B*58:01 and presented with symptoms after taking alternative medicine (benzbromarone; table 2). None of the participants was diagnosed with SCARs, as defined by the RegiSCAR Group (main characteristics included multisystemic involvement and frequent eosinophilia). Other adverse events were fever, sore throat, fatigue, dizziness, insomnia, and gastrointestinal symptoms. These adverse events were found in both HLA-B*58:01 positive and negative participants. There was no significant correlation between specific symptoms and HLA-B*58:01 status (table 2).

Estimates of expected historical incidence of SCARs

Records from the National Health Insurance research database revealed that allopurinol was prescribed for at least three months for 137 380 people in 2001, 117 896 in 2002, 107 873 in 2003, and 102 060 in 2004 who had not previously taken allopurinol—dating back to at least the beginning of the previous calendar year (table 3). We then compared historical incidence of allopurinol induced SCARs in 2001, 2002, 2003, and 2004 with the incidence seen in study participants. Our estimated incidence of SCARs among allopurinol users in 2001, 2002, 2003, and 2004 in Taiwan were therefore 0.32%, 0.30%, 0.28%, and 0.29%, for each year in 2001-04, respectively. The mean estimated incidence (0.30% per year, 95% confidence interval 0.28% to 0.31%) was used as the historical incidence for further analysis.

Incidence of SCARs after genetic screening

Based on the estimated historical incidence of 0.30% per year, we expected seven cases of drug rash with eosinophilia and systemic symptoms, Stevens-Johnson syndrome, and toxic epidermal necrolysis among the 2173 participants in our study who took allopurinol. However, none of these disorders was found for any of the participants, which differed significantly from the historical incidence (P=0.0026, using the two side, one sample binomial test; table 3).

Discussion

Principal findings

Our results indicate that screening Han Chinese patients for HLA-B*58:01 allele before initiating allopurinol treatment, and then withholding allopurinol from those who carry the allele would likely reduce the incidence of allopurinol induced SCARs. In the present study, adverse cutaneous reactions (including oral lesions and rash) that developed in the participants were mild, transient, and localised. In addition, under continuous and systematic monitoring of dermatological

Table 2 | Adverse events during two month follow-up

Adverse event	HLA-B*58:01 positive participants receiving alternative drug treatment (n=354)	HLA-B*58:01 negative participants receiving allopurinol (n=2173)	Total (n=2910)
Mild cutaneous events			
Rash and itching	3*	94	97
Blisters	0	0	0
Oral ulcers	0	2	2
Rash, itching, oral ulcers, and fever	0	1	1
Rash, itching, and other adverse events	0	22	22
Severe cutaneous events			
Drug reaction with eosinophilia and systemic symptoms	0	0	0
Urticaria	0	0	0
Stevens-Johnson syndrome or toxic epidermal necrolysis	0	0	0
Other adverse events†			
Fever	0	1	1
Sore throat	0	2	2
Fatigue	0	5	5
Other	20	117	137

Data are no of participants having adverse events.
*All three participants took benzbromarone.
†Each participant may have had more than one adverse event. Adverse events with a low frequency are not listed.

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Table 3 | Historical incidence of allopurinol induced SCARs in 2001-04, compared with incidence among study participants

Variable	Year			
	2001	2002	2003	2004
No of new recipients of allopurinol	137 380	117 896	107 873	102 060
No of participants with allopurinol induced SCARs	438	348	307	295
Incidence (%) of allopurinol induced SCARs (95% CI)	0.32% (0.29% to 0.35%)	0.30% (0.27% to 0.33%)	0.28% (0.25% to 0.32%)	0.29% (0.26% to 0.32%)
P value comparing historical incidence and actual incidence among study participants*	0.0018	0.0026	0.0038	0.0040

SCARs=severe cutaneous adverse reactions.
*P values calculated by the two side, one sample binomial test.

symptoms, many HLA-B*58:01 negative patients with transient and mild skin lesions resumed taking allopurinol without a recurrence of symptoms.

We did not identify any participants with SCARs, which indicates that the incidence of allopurinol induced SCARs in HLA-B*58:01 negative patients is quite low. So far, all study participants have been followed up for at least nine months, and no cases of SCARs have been reported. Hence, in this cohort, the incidence of SCARs at two month follow-up is the same as the incidence after nine months. Moreover, we attempted to identify SCARs in our prospective cohort by searching Taiwan's National Health Insurance research database using the unique identification numbers of individual Taiwanese patients; no SCARs were identified by this approach. Therefore, occurrence of allopurinol induced SCARs could be successfully prevented by the use of a genetic screening protocol.

Our results lend support to the use of HLA-B*58:01 screening to prevent allopurinol induced SCARs.[32] However, as for any new pharmacogenomic test, the use and safety of any alternative drug treatments must be documented. Of 569 HLA-B*58:01 carriers in the present study, 354 (62%) were given alternative treatment, whereas the other carriers continued to take their pre-study medication (such as colchicine and non-steroidal anti-inflammatory drugs). Among the 354 HLA-B*58:01 carriers treated with an alternative drug, the only symptom documented during the two month follow-up was mild, transient rash in three (1%) participants.

Implications for clinical practice

In addition to the safety benefit to patients, HLA-B*58:01 screening could also be considered a cost effective intervention. Many medical societies worldwide, including the American College of Rheumatology, currently recommend the use of a xanthine oxidase inhibitor with either allopurinol or febuxostat as first line treatment for hyperuricaemia.[29] Benzbromarone is a uricosuric compound that has been used to control hyperuricaemia. It is effective in lowering levels of serum uric acid, especially in patients with low urate excretion. However, benzbromarone has a risk of severe hepatotoxicity as well as acute renal colic, and the drug has been withdrawn from the market or has not been available in some countries (including the United States and some European countries).[33] These are the main reasons why benzbromarone or other uricosuric compounds have not been given to all patients with gout.[34]

There are two potential treatment strategies against gout, which have identical therapeutic efficacy but different costs for government and society. One strategy is global substitution of allopurinol with the new xanthine oxidase inhibitor, febuxostat; the other is to use allopurinol for patients who are HLA-B*58:01 negative and substitute allopurinol with febuxostat in patients who are HLA-B*58:01 positive.

Recently, cost effectiveness analyses carried out in Thai and Korean populations suggested that HLA-B*58:01 testing is a more cost effective measure than global substitution of febuxostat for allopurinol.[35 36] Because the negative predictive value of HLA-B*58:01 for allopurinol induced SCARs is 100%, the risk of developing allopurinol induced SCARs among HLA-B*58:01 negative patients would be very low. In view of the cost effectiveness or efficacy of other drug treatments for similar indications, not prescribing allopurinol to HLA-B*58:01 positive patients is likely to be prudent, despite the low estimated positive predictive value (2%) of the test.

Potential impact of study findings

In the present study, prospective screening by HLA-B*58:01 genotyping before allopurinol treatment in 2926 people with an indication for allopurinol treatment could successfully reduce the incidence of allopurinol induced SCARs (from seven expected cases of SCARs to none in the 2173 patients who took allopurinol). These results suggest that HLA-B*15:02 screening of about 110 000 new users of allopurinol in Taiwan each year could prevent about 330 cases of allopurinol induced SCARs every year.

Based on our previous experience, this expectation of impact is reasonable. Carbamazepine, which used to be the most common drug causing Stevens-Johnson syndrome and toxic epidermal necrolysis in Taiwan, is now only the eighth most common drug causing these life threatening conditions. This change is attributable to our previous prospective study showing that screening of the allele HLA-B*15:02 could reduce the incidence of carbamazepine induced Stevens-Johnson syndrome or toxic epidermal necrolysis.[30] Subsequent coverage of the genotyping by the Taiwan's National Health Insurance system led to nationwide screening for HLA-B*15:02 by the medical community.

Strengths and limitations of study

The development of a reliable pharmacogenomics based approach to prevent adverse reactions with

severe complications is a good example to demonstrate that the concept of personalised medicine can be a clinical reality. So far, there have been three critical findings involving adverse drug reactions: allele HLA-B*15:02 for carbamazepine induced Stevens-Johnson syndrome or toxic epidermal necrolysis; HLA-B*57:01 for abacavir induced drug hypersensitivity; and as seen in the present study, HLA-B*58:01 for allopurinol induced SCARs.

These findings show the potential benefits of genetic testing to prevent adverse drug reactions in the clinical setting owing to extremely high negative predictive values. To achieve this goal, solid evidence collected from different clinics and based on reliable laboratory tests is essential, as well as the development of effective strategies to incorporate these tests into routine practice. More importantly, a prospective study to demonstrate that these relevant processes can be performed in clinical settings is also needed. Therefore, the PREDICT-1 study team and our group investigated the use of a prospective screening approach to prevent abacavir induced drug hypersensitivity in 2008[37] and carbamazepine induced Stevens-Johnson syndrome or toxic epidermal necrolysis in 2011.[30]

Compared with the use of other HLA alleles as biomarkers for preventing drug hypersensitivity, HLA-B*58:01 can be used in a broader spectrum of ethnic groups. The strong association between HLA-B*58:01 and allopurinol induced SCARs has been found in ethnic groups other than the Han Chinese, including Thai, Japanese, Korean, and European groups.[16-18 20 21 38] Studies in Taiwan, Japan, Europe, and Israel have shown that allopurinol is now a major cause of drug induced SCARs.[11-13]

In countries where the HLA-B*58:01 is relatively prevalent (for example, the carrier prevalence among Taiwanese population with HLA-B*58:01 is 20%) and where a tight association has been found, screening for this allele could be beneficial for preventing allopurinol induced SCARs. However, the implementation of HLA-B*58:01 screening certainly requires caution in some populations, such as Japanese and European groups, because not all patients with allopurinol induced SCARs carry the allele in those populations.[21 38] Furthermore, in countries where the allele frequency is low (about 1%), restricting the screening for this allele to a more high risk group of patients (for example, chronic renal failure) could also be a strategy for preventing SCARs.[14 39]

For countries or populations in which the prevalence is ill defined, further studies to estimate the prevalence are suggested for possible use of this screening. In addition, because the association between the HLA-B*58:01 allele and mild cutaneous adverse reaction induced by allopurinol has been found in mainland China,[19] future investigations might be needed to examine whether screening for the HLA-B*58:01 allele could reduce the prevalence of allopurinol induced maculopapular eruption.

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Contributors: Equal contribution: (corresponding authorship) J-YW, Y-TC, and C-YS; (first authorship) T-MK, C-YT, S-YC, K-SC, and K-HY. C-YS was the study supervisor. J-YW, Y-TC, and C-YS obtained funding and formulated the research question. T-MK, C-HC, J-YW, Y-TC, and C-YS were involved in the study conception and design. C-YT, S-YC, K-SC, K-HY, C-SC, C-MH, C-RW, C-TW, C-LY, S-CH, J-CT, W-TL, W-CT, G-DY, T-TO, K-HC, J-HY, T-LL, T-HL, D-YC, P-JH, M-YW, Y-MC, C-HC, M-FL, H-WY, J-JL, M-CK, C-CW, S-YH, S-FL, H-PC, Y-CC, H-TL, C-WW, C-LH, C-SC, and C-SW provided study materials or patients collected and collated data. T-MK, Y-HY, and Y-CC were involved in analysis and interpretation of the data. Y-HY, Y-CC, and C-HC provided statistical expertise. T-MK and C-YS wrote the first draft of the manuscript. T-MK, K-HY, C-HC, J-YW, Y-TC, and C-YS revised it critically for important intellectual content. T-MK, M-TML, PC, and J-YW provided administrative, technical, or material support. All authors approved the final version. T-MK, J-YW, Y-TC, and C-YS are the guarantors. T-MK, C-YT, S-YC, K-SC, and K-HY contributed equally to this article. The web appendix lists other members of the Taiwan Allopurinol-SCAR Consortium.

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Data sharing: Details of how to obtain additional data from the study (such as technical appendix, statistical programming) are available from the corresponding author at bmcys@ibms.sinica.edu.tw.

The lead author (the manuscript's guarantor) affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

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Web appendix: Supplementary material