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HLA-B*58:01 genotyping to prevent allopurinol-induced severe cutaneous adverse reactions: national prospective study

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HLA-B*58:01 genotyping to prevent allopurinol-induced severe cutaneous adverse reactions: national prospective study

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ABSTRACT

OBJECTIVE: To evaluate the impact of using prospective HLA-B*58:01 screening to identify at-risk subjects for preventing life-threatening severe cutaneous adverse reactions (SCARs) induced by allopurinol, which is one of the common causes of SCARs.

DESIGN: Prospective cohort study.

SETTING: 15 medical centers in different geographic regions of Taiwan, from July 2009 through August 2014.

PARTICIPANTS: We recruited 2926 subjects who had an indication for allopurinol treatment but had not taken allopurinol previously.

MAIN OUTCOME MEASURES: The incidence of allopurinol-induced SCARs with and without screening.

RESULTS: DNA purified from each subject's peripheral blood was used to assess the presence of allele HLA-B*58:01. Subjects who tested positive (19.6% of the total) were advised to avoid allopurinol and were referred to an alternate medication or advised to continue with their pre-study medication for gout; those testing negative (80.4%) were given allopurinol. Subjects were interviewed once a week for 2 months to monitor symptoms. The estimated historical incidence of allopurinol-induced SCARs was used for comparison. Mild, transient rash without blisters developed in

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3.3% of subjects during follow-up. None of the subjects were hospitalized owing to adverse drug reactions. SCARs did not develop in any of the HLA-B*58:01-negative subjects receiving allopurinol; this is in contrast to the 7 expected cases of SCARs based on the estimated historical nationwide incidence of allopurinol-induced SCARs (0.30%; $P = 0.0026$; Fisher's two-tailed exact test).

CONCLUSIONS: Identification of subjects carrying allele HLA-B*58:01 and the absence of allopurinol therapy for these subjects were strongly associated with decreased incidence of allopurinol-induced SCARs.

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INTRODUCTION

Developing a reliable pharmacogenomics-based approach to prevent adverse reactions with severe complications is a major goal of personalized medicine[1-3]. Severe cutaneous adverse reactions (SCARs) constitute a set of life-threatening conditions that include drug rash with eosinophilia and systemic symptoms (DRESS), Stevens–Johnson syndrome (SJS), and toxic epidermal necrolysis (TEN)[4]. 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 characterized by a severe idiosyncratic reaction in skin, blistering exanthema of macular papules, or mucosal involvement[6]. The most severe condition of SCAR/TEN is rather lethal (up to 35%).

Allopurinol, a first-line prescription medication for gout and hyperuricemia[7-10], is one of the most common causes of SCARs in Asia and Europe[11-13]. Through 2012, the literature reported approximately 1000 subjects who had allopurinol-induced SCARs; these patients represented multiple ethnicities and geographic regions[12]. Although allopurinol has SCARs-related risks and other anti-gout medicines are available, allopurinol is still a common treatment for gout and hyperuricemia owing to its relative low cost, efficacy, and convenience.

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We have reported that allopurinol-induced SCARs correlate strongly with allele human leukocyte antigen (HLA)-B*58:01 in Han Chinese populations[14], as confirmed in Han Chinese from Hong Kong and mainland China and in Japanese, Korean, Thai, and other Asian populations as well as European and Portuguese populations[15-21]. Among subjects 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. HLA-B*58:01 can present the allopurinol metabolite, oxypurinol, directly to cytotoxic T cells without antigen processing[22-24]. More importantly, allopurinol/oxypurinol-specific T cell–mediated cytotoxicity is restricted to carriers of HLA-B*58:01[23,24].

Based on our previous findings[14], an extremely high risk (odds ratio, 580.3; 95% confidence interval, 34.4–9780.9; $P = 4.7 \times 10^{-24}$) to develop allopurinol-induced SCARs was found in Han Chinese who carry HLA-B*58:01 compared with those who do not carry this allele. Hence, if HLA-B*58:01 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%, HLA-B*58:01 would have a negative predictive value of 100.0% and a positive predictive value of 2.0%. Thus, the use of HLA-B*58:01 genotyping to prevent allopurinol-induced SCARs in routine clinical practice appears warranted. We

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therefore sought to determine whether prospective screening via HLA-B*58:01 genotyping prior to allopurinol treatment could reduce the incidence of allopurinol-induced SCARs.

METHODS

Study Design

Because of tight association of HLA-B*58:01 and the life-threatening allopurinol-induced SCARs, the study was designed as a nonrandomized study, using historical incidence as a control. We recruited subjects from 15 participating hospitals throughout Taiwan (see author affiliation and **Supplementary Appendix**). There were 9 points of interaction with HLA-B*58:01–negative subjects and 10 points of interaction with HLA-B*58:01 carriers, namely the initial screening visit, a second clinic visit for HLA-B*58:01 carriers, and telephone interviews for both groups weekly during the 2-month follow-up. Subjects aged 6 months to 99 years who had not previously taken allopurinol within 3 months were recruited. In accordance with clinical indications at the time of screening, these subjects would have received allopurinol and thus were invited to participate in the study. The efficacy of all the medicines for reducing uric acid level was evaluated based on the guideline for the management of gout[8-10].

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

We prescribed and dispensed allopurinol to all subjects at the initial screen, but we asked that each subject defer taking allopurinol until the HLA-B*58:01 genotyping results were finalized. 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 3 days.

HLA-B*58:01–positive subjects were asked to return to their respective hospitals within 3 days. We then explained their risk of allopurinol-induced SCARs and recommended that they take alternative medicine. HLA-B*58:01–negative subjects (who also were counseled about SCARs risk) were started on allopurinol. In general, SCARs onset occurs within 2 months after the initiation of allopurinol therapy[25]; we therefore interviewed all subjects by telephone during the 2-month period following initial screening (for HLA-B*58:01–negative subjects) or after the second clinic visit (for HLA-B*58:01–positive subjects) to monitor for symptoms of adverse drug reactions, including SCARs. If early symptoms of SCARs developed, a subject was

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asked to return to the clinic immediately for dermatological evaluation. We monitored all subjects throughout the study's duration, with the exception of 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 and the institutional review board at each participating clinic approved the study. We obtained written informed consent from all subjects or from parents or guardians for subjects who were ≤ 21 years of age.

Genotyping of HLA-B*58:01

Whole blood (2 ml) was collected from each subject in a Monovette tube that was 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 system (Qiagen). The presence or absence of HLA-B*58:01 was determined with the PG5801 DNA detection kit (Pharmigene). The kits are based on a real-time PCR with sequence-specific primers for HLA-B*58:01. To confirm the genotyping results, the first 900 samples were also examined in parallel with an HLA sequence–specific oligonucleotide reverse line blot (Dynal Biotech); the results were consistent in each sample.

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Annual Incidence

The estimated number of SCARs cases was based on diagnostic code 695.1 in both the International Classification of Diseases, 9th Revision, and Clinical Modification (ICD-9-CM), which are commonly used in studies of adverse drug reactions[26,27]. The ICD-9-CM 695.1 code covers all SCARs, including DRESS, SJS, and TEN. The number of subjects having this code was determined from the National Health Insurance Research Database (NHIRD), as provided by the National Health Insurance Administration of Taiwan. NHIRD is nationwide and derived from the claims data of the National Health Insurance program created in 1995, now covering over 99% of the Taiwanese population. 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.

Because it commonly takes weeks to months for SCARs to develop after the initiation of treatment, from NHIRD we obtained data on the number of persons who obtained a new 3-month prescription for allopurinol for each of years 2001, 2002, 2003, and 2004.

Owing to the established close association between HLA-B*58:01 and potentially lethal allopurinol-induced SCARs, this study was approved by our

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Institutional Review Board as a nonrandomized study, using historical incidence as a control. The historical incidence of allopurinol-induced SCARs was estimated based on data obtained from NHIRD, and NHIRD is very reliable and applicable for nationwide studies in Taiwan[28-30]. The Taiwanese government established NHIRD when the National Health Insurance system was launched in 1995. NHIRD is single-payer health insurance plan managed by the Taiwanese government, and it provides healthcare for nearly all Taiwanese (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 NHIRD are therefore comprehensive.

Statistical Analysis

Based on the prevalence of allele HLA-B*58:01 (20%) in the Han Chinese population residing in Taiwan[31], we calculated that 2169 subjects would provide a power of 99% to detect a reduction in the incidence of allopurinol-induced SCARs from 0.30% (i.e., 30 cases per 10,000 new recipients) to 0.03%. Fisher's exact test was used to compare the rate of allopurinol-induced SCARs in the prospective screening population with historical incidence. All P values are two-tailed, and a $P < 0.05$ was considered statistically significant.

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RESULTS

Subjects

From July 2009 through August 2014, we enrolled 2926 subjects, 2910 of which underwent genotyping and were included in the 2-month follow-up (**Figure 1**). Male and female subjects accounted for 82.8% and 17.2%, respectively, with mean age 54.9 years (range, 14–99) (**Table 1**). Indications for allopurinol treatment included chronic tophaceous gout (35.2% of subjects), hyperuricaemia (23.9%), chronic tophaceous gout plus hyperuricaemia (16.1%), chronic tophaceous gout plus other conditions (7.4%), and other conditions (17.4%) (**Table 1**).

Screening for HLA-B*58:01

Among the 2910 enrolled subjects, 571 (19.6%) were identified as having allele HLA-B*58:01 and were given advice not to take allopurinol; these subjects were prescribed alternative drugs or given advice to continue taking their pre-study medication. Of these subjects, we monitored for adverse events and found that 2 were lost during follow-up, 354 took an alternative medication, and 215 took their pre-study medication (**Figure 1**). Alternative medications were benzbromarone, bisoprolol fumarate, bromhexine hydrochloride, brompheniramine, colchicine, febuxostat, hydroxychloroquine, sulfasalazine, sulfonylurea, and sulfinpyrazone

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(**Supplementary Table 1**). The remaining 2339 subjects (80.4%) were negative for HLA-B*58:01. Among them, 155 did not take allopurinol and 11 were lost during follow-up, leaving 2173 HLA-B*58:01–negative subjects who took allopurinol and were monitored (**Figure 1**).

Adverse Events Monitoring

Of all 2910 subjects, mild and transient rash and itching developed in 97 (3.3%), but none had a combination of rash, itching, and localized blisters (**Table 2**). Among the 97 subjects with rash or itching, 3 were found to carry HLA-B*58:01 and presented with symptoms after taking alternative medicine (benzbromarone) (**Table 2**). None of the subjects was diagnosed with SCARs as defined by the RegiSCAR Group (main characteristics including multi-systemic 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 subjects. There was no significant correlation between specific symptoms and whether a patient was HLA-B*58:01–positive or –negative.

Estimating the Expected Historical Incidence of SCARs

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NHIRD data revealed that allopurinol was prescribed for at least 3 months for 137,380 persons in 2001, 117,896 persons in 2002, 107,873 in 2003, and 102,060 in 2004 who had not previously taken allopurinol—at least dating back to the beginning of the previous calendar year (**Table 3**). Historical incidence of allopurinol-induced SCARs in 2001, 2002, 2003, and 2004 was then compared with the incidence seen in study subjects. Our estimated incidence of SCARs among allopurinol users in 2001, 2002, 2003, and 2004 in Taiwan was thus 0.32%, 0.30%, 0.28%, and 0.29%, respectively. The mean (0.30%) was used as the historical incidence for further analysis.

Incidence of SCARs after Genetic Screening

Based on the estimated historical incidence of 0.30%, 7 cases of DRESS, SJS, or TEN were to be expected among our 2173 subjects who took allopurinol. However, no case of DRESS, SJS, or TEN was found for any of the subjects, which differed significantly from the historical incidence ($P = 0.0026$, Fisher's exact test) (**Table 3**).

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DISCUSSION

Principal findings

Our results indicate that screening Han Chinese patients for allele HLA-B*58:01 before initiating allopurinol therapy and then withholding allopurinol from HLA-B*58:01–positive patients could reduce the incidence of allopurinol-induced SCARs. In the present study, adverse cutaneous reactions, including oral lesions and rash, that occurred in the subjects were mild, transient, and localized. In addition, under continuous and systematic monitoring of dermatological symptoms, many HLA-B*58:01–negative subjects with transient and mild skin lesions resumed taking allopurinol without a recurrence of symptoms. Notably, we did not identify any subject with SCARs, which supports data indicating that the incidence of allopurinol-induced SCARs in HLA-B*58:01–negative persons is quite low.

Our results suggest the merit of HLA-B*58:01 screening to prevent allopurinol-induced SCARs. As for any new pharmacogenomic test, however, the use and safety of the alternative medication(s) must be documented. Of the 569 HLA-B*58:01 carriers, 354 (62.2%) were given alternative treatment, whereas the other carriers continued to take their pre-study medication such as colchicine and nonsteroidal anti-inflammatory drugs. Among the 354 HLA-B*58:01 carriers treated

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with an alternate therapy, the only symptom documented during the 2-month follow-up was mild, transient rash in 3 subjects (0.8%).

Implications for clinical practice

In addition to saving the lives of patients and saving medical costs associated with SCARs, HLA-B*58:01 screening could also be considered a potentially cost-effective intervention. With regard to patients with gout, there are two potential treatment strategies with identical therapeutic efficacy but with different costs for government and society. One strategy is global substitution of allopurinol with the new xanthine oxidase inhibitor, febuxostat. The other strategy is to substitute allopurinol with febuxostat based on HLA-B*58:01 screening. We utilized economic impact analysis to compare the real cost to national health insurance and to the nation overall imparted by the two aforementioned drug-use strategies. To estimate the expenditure to National Health Insurance in Taiwan, we performed an analysis based on the cost of drug purchase and HLA-B*58:01 screening (**Supplementary Table 2**). We found that applying HLA-B*58:01 screening for drug compatibility reference could reduce health expenditures by up to $12,350,187 (US dollars, estimated based on drug cost in Taiwan) annually compared with a global substitution of febuxostat for allopurinol. Similarly, cost-effectiveness analyses carried out for Thai and Korean

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populations also suggest that applying HLA-B*58:01 testing can save costs compared with a global substitution of febuxostat for allopurinol[32,33]. 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 extremely low. Considering the cost-effectiveness or efficacy of other medications for similar indications, avoiding prescription of allopurinol for HLA-B*58:01-positive patients is likely prudent, despite the low estimated positive predictive value (2%) of the test.

Potential impact of this study

In the present study, prospective screening by HLA-B*58:01 genotyping prior to allopurinol treatment in 2926 subjects who had an indication for allopurinol treatment could successfully reduce the incidence of allopurinol-induced SCARs (from 7 expected cases of SCARs to none in the 2173 patients who took allopurinol), which may have a huge impact on reducing the number of patients with allopurinol-induced SCARs in the population. Based on our previous experience, this expectation of impact is reasonable. Carbamazepine, which formerly was the leading culprit drug causing SJS/TEN in Taiwan, is now down to the number eight in the list of drugs causing these life-threatening conditions. This is attributable to our previous

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prospective study showing that HLA-B*15:02 screening could reduce the incidence of carbamazepine-induced SJS/ TEN[30] with subsequent Taiwan's National Health Insurance coverage of the genotyping, which led to wide screening for HLA-B*15:02 by the medical community.

Strengths and limitations of study

Developing a reliable pharmacogenomics-based approach to prevent adverse reactions with severe complications is one of best examples to demonstrate that the concept of personalized medicine can be a clinical reality. To date, in adverse drug reactions (ADR), there are 3 critical findings, including HLA-B*15:02 for carbamazepine-induced Stevens-Johnson syndrome and toxic epidermal necrolysis (SJS/TEN), HLA-B*57:01 for abacavir-induced drug hypersensitivity, and HLA-B*58:01 for allopurinol-induced severe cutaneous adverse reactions, showing a high potential to apply this concept of genetic testing to prevent ADR in clinic due to the extremely high negative predictive values. To this end, solid evidence collected from different clinics based on reliable laboratory tests, and showing effective strategies to incorporate these tests into routine practice is essential. More importantly, a prospective study to demonstrate all of these can be performed in clinical settings is critically essential. Therefore, the PREDICT-1 Study Team and our group have

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provided such strong and important evidences by using a "prospective-screening" approach to prevent abacavir-induced drug hypersensitivity in 2008[34] and carbamazepine-induced SJS/TEN in 2011[30], respectively. The present study we reported here is the third case, i.e. the use of HLA-B*58:01 genotyping to prevent allopurinol-induced severe cutaneous adverse reactions. Compared with other HLA alleles as biomarkers for preventing drug hypersensitivity, HLA-B*58:01 has the potential to be applied in a broader spectrum of ethnicities. Specifically, the strong association between HLA-B*58:01 and allopurinol-induced SCARs has been found for ethnicities other than Han Chinese, including Thai, Japanese, Korean, European, and Portuguese[16-18,20,21,35]. In Taiwan, Japan, Europe, and Israel, studies have shown that allopurinol is now the major cause of drug-induced SCARs[11-13]. Our results suggest that in countries where HLA-B*58:01 is relatively prevalent (e.g. the allele frequency of HLA-B*58:01 in the Taiwanese population is 10%, and the carrier prevalence among subjects with HLA-B*58:01 is 20%), HLA-B*58:01 screening could be beneficial for preventing allopurinol-induced SCARs; in countries where allele frequency of HLA-B*58:01 is relatively low (<1%), HLA-B*58:01 screening in a more specialized population (i.e., chronic renal failure) also could be a potential way to prevent SCARs. In addition, because the association between the HLA-B*58:01 allele and mild cutaneous adverse reaction induced by allopurinol has been found in

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mainland China[19], future investigations may be needed to examine whether screening for the HLA-B*58:01 allele can reduce the prevalence of allopurinol-induced maculopapular eruption (MPE).

CONCLUSION

Because the contribution of HLA-B*58:01 to allopurinol-induced SCARs is causal[14,23,24], the present prospective study with a large number of study subjects provides a strong basis for routine testing for this allele as well as for general implementation of personalized medicine testing.

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Figure 1. Enrollment and Outcomes.
Allopurinol was prescribed and provided for all subjects at the time of the screening visit, but patients were asked to defer taking the drug until the results of genetic testing were available. All subjects, regardless of HLA-B status, were followed for 2 months, with weekly telephone interviews.

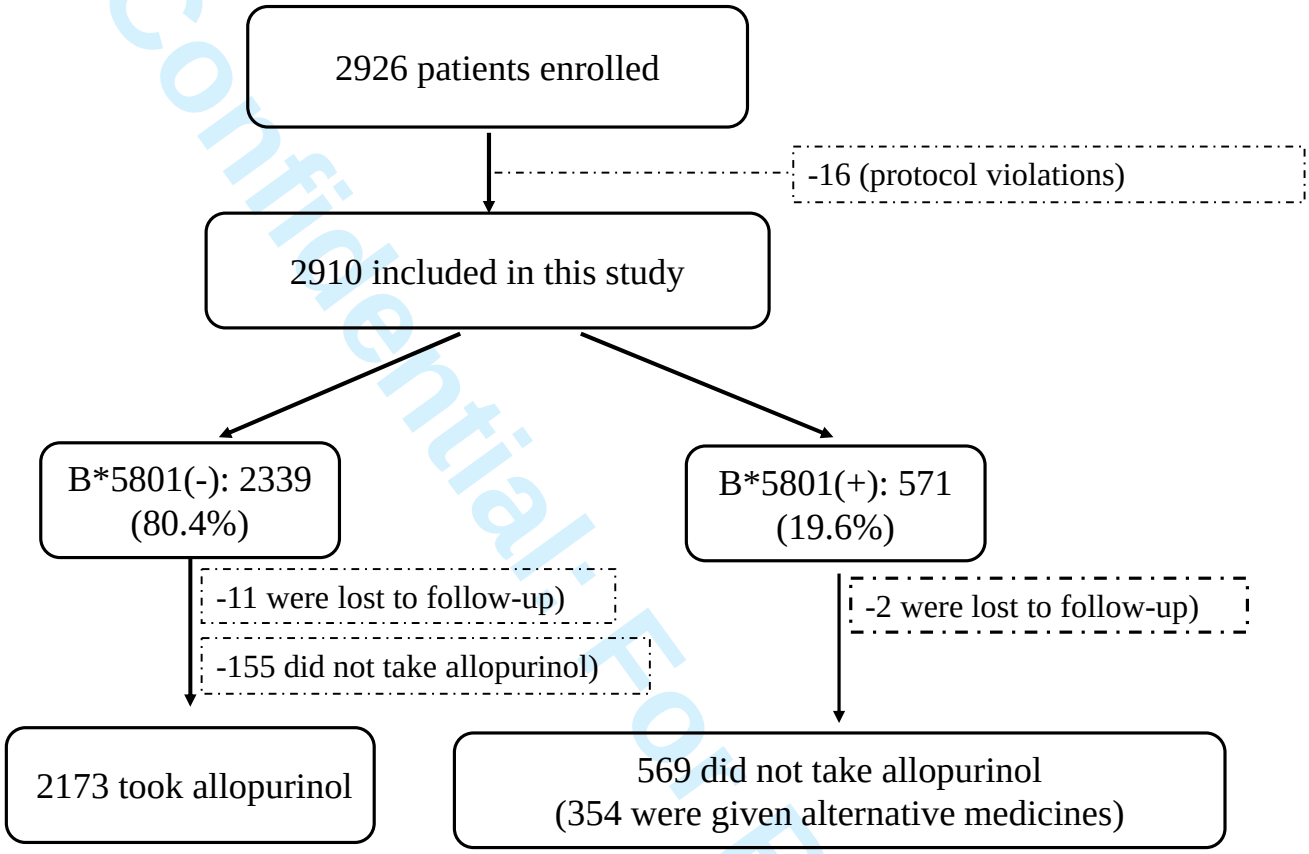

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Table 1. Subject description

Characteristic	HLA-B*58:01-Positive (N=571)	HLA-B*58:01-Negative (N=2339)	Total (N=2910)
Gender—no. (%)			
Male	460 (80.6)	1950 (83.4)	2410 (82.8)
Female	111 (19.4)	389 (16.6)	500 (17.2)
Age—yr			
Mean	54.8	54.9	54.9
Range	19–99	14–95	14–99
Kidney function			
Renal insufficiency	120	444	564
Indication for allopurinol—no. (%)			
Chronic tophaceous gout	204 (35.7)	820 (35.1)	1024 (35.2)
Hyperuricaemia	141 (24.7)	555 (23.7)	696 (23.9)
Chronic tophaceous gout; hyperuricaemia	97 (17.0)	371 (15.9)	468 (16.1)
Chronic tophaceous gout; other	43 (7.5)	173 (7.4)	216 (7.4)
Other conditions*	86 (15.1)	420 (18.0)	506 (17.4)

* These conditions include urate nephropathy, prevention of recurrent nephrolithiasis, and prevention of recurrent calcium oxalate stones.

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Table 2. Adverse events during the 2-month follow-up

Adverse Event	HLA-B*58:01-Positive with Alternative Medication (N=354)	HLA-B*58:01-Negative with Allopurinol (N=2173)	Total
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

*Among these three subjects, the alternative drug was benzbromarone.
†Subjects 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, 2002, 2003, and 2004, as compared with the incidence among study subjects

Variable	2001	2002	2003	2004
New recipients of allopurinol (no.)	137380	117896	107873	102060
Allopurinol-induced SCARs* (no.)	438	348	307	295
Incidence of allopurinol-induced SCARs (%)	0.32%	0.30%	0.28%	0.29%
P value for comparison between historical incidence and incidence among study subjects†	0.0027	0.0037	0.0057	0.0035

*SCARs: Severe cutaneous adverse reactions.
†All *P* values were calculated with the use of Fisher's exact test.

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Supplementary Appendix

The following institutions and investigators, in addition to the authors, participated in the Taiwan Allopurinol-SCAR consortium are as follows:

Institute of Biomedical Sciences, Academia Sinica: Pei Chen

Kaohsiung Medical University Chung-Ho Memorial Hospital: Wen-Chol Voon, Kun-Tai Lee, Hsiang-Chun Lee, Po-Chao Hsu, Hung-Chun Chen, Jin-Yuh Guh, Shang-Jyh Hwang, Shin Shyi Jang, Kun Der Lin, Hsuan-Fu Kuo, Sheng-Wen Niu.

National Taiwan University Hospital: Chih-Chao Yang.

Chang Gung Memorial Hospital: Yung-Chiao Wu Chan, Chung Lee, Yao-Fan Fang, Chang-Fu Kuo, Chen-Hung Lai.

The Tri-Service General Hospital: Hsiang-Cheng Chen, San-Yuan Kuo, Tsung-Yun Hou, Feng-Cheng Liu.

E-Da Hospital: Li-Chun Ho, Yi-Jer Lee, Min-Yu Chang, Yi-Ting Chen, Ho-Ching Chen.

Institute of Medicine, Chung Shan Medical University: Cheng-Chung Wei, Gregory-Jiazer Tsay, Pei-Ying Liang.

Supplementary Table 1.
Alternative medicines for HLA-B*58:01-postive individuals

Alternative medicines	N *	%
ANSRON	1	0.27
BENZBROMARONE	256	69.19
BENZBROMARONE+COLCHICINE	6	1.62
BENZBROMARONE+SULFIN	1	0.27
BISOPROLOL FUMARATE	1	0.27
BROMHEXINE HCL	3	0.81
BROMPHEIRAMINE	16	4.32
COLCHICINE	21	5.68
COLCHICINE+BROMPHEIRAMINE	1	0.27
COLCHICINE+EURICON	1	0.27
FEBURIC	27	7.30
FEBURIC FC	1	0.27
FEBURIC+COLCHICINE	1	0.27
FEBUXOSTAT	3	0.81
FEBUXOSTAT F.C.	1	0.27
NOGOUT	4	0.81
SALAZINE EC+PLAQUENIL	1	0.27
SULFANILYLUREA	1	0.27
SULFIN	1	0.27
SULFINPYRAZONE	17	4.59
URINORM	5	1.35
URISUE	1	0.27
Total	**370**	**100.00**

*Some patients took multiple alternative medicines.

Supplementary Table 2.
Cost-effectiveness analysis for substituting febuxostat for allopurinol based on the drug cost in Taiwan

For individual

Long-term user (1 yr+)		Annual Drug Cost (NT$)
allopurinol (300 mg, NT$ 2.94)*	1 pills/day x 365	1,073
febuxostat (80 mg, NT$ 25.10)*	1 pills/day x 365	9,162

	Test cost (NT$)	Original drug cost (NT$)	New drug cost (NT$)	
For HLA-B*5801 tested patients	3,285†	1,073 (If B*5801(-))	9,162	
First year saving (NT$)				4,803
2nd year & future saving (NT$)				8,088

For group health care providers (116,302 users annually)

	With HLA-B*58:01 test		Without HLA-B*58:01 test	
		(NT$)		(NT$)
Drug: allopurinol	80%	99,842,941		
Drug: febuxostat	20%	213,100,155	100%	1,065,500,773
Cost of genetic test		382,052,070		
Annual total cost		694,995,166		1,065,500,773
Annual Savings (NT$):		**370,505,607**		
Annual Savings (US$):		**12,350,187**		

*The cost of allopurinol and febuxostat is based on the payment indicated in the Taiwan National Health Insurance.

†The cost of HLA-B*58:01 genotyping is referred according to the payment of HLA-B*15:02 genotyping indicated in the Taiwan National Health Insurance.