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Original Article

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ABSTRACT

Background: The HLA-B*58:01 allele is a significant genetic risk factor for allopurinol-induced cutaneous adverse drug reactions (CADRs), including mild and severe cutaneous adverse drug reactions(MCARs and SCARs, respectively). In Thailand, the HLA-B*58:01 screening test is not mandatory for all patients, resulting in suboptimal screening rates. In addition, there is a lack of studies on the impact of the screening test on clinical and economic outcomes. **Objectives:** This study aimed to determine if the HLA-B*58:01 screening test could prevent CADRs and reduce direct medical costs. **Materials and Methods:** This retrospective cohort study was conducted at Charoenkrung Pracharak Hospital in Bangkok. A total of 1026 available medical records of patients with gout or asymptomatic hyperuricemia, recorded between January 1, 2019, and December 31, 2023, were reviewed. The incidence of CADRs, MCARs, and SCARs among patients who underwent (study group) or did not undergo (comparison group) the test was compared. **Results:** There were 281 and 745 patients in the study and comparison group, respectively. In the study group, 53 patients had a positive outcome for HLA-B*58:01 and refrained from allopurinol, except for two cases that received the drug before the test, while 163 of the 228 who tested negative received allopurinol. All patients in the comparison group received allopurinol. The incidences of CADRs and MCARs in the study group were statistically lower than the comparison group (1.4% vs. 5.9%, $P = 0.007$, and 1.4% vs. 5%, $P = 0.02$, respectively). No significant differences in the incidence of SCARs were observed (0% vs. 0.9%; $P = 0.216$). The direct medical costs of the study group were less than the comparison group, for 2,128.43 US dollars per person. **Conclusion:** The screening of HLA-B*58:01 before initiating allopurinol effectively prevented allopurinol-induced CADRs and was cost-effective.

Key words: Allopurinol hypersensitivity, allopurinol-induced cutaneous adverse drug reactions, HLA-B*58:01, medical costs

INTRODUCTION

Drug hypersensitivity or drug allergy is an unpredictable response to medication that can cause unwanted consequences to patients and the healthcare system.[1,2] Most drug hypersensitivities manifest as cutaneous adverse drug reactions (CADRs), which can be further categorized into mild cutaneous adverse drug reactions (MCARs) such as maculopapular eruption (MPE), and severe cutaneous adverse drug reactions (SCARs) including Stevens-Johnson syndrome

(SJS), toxic epidermal necrolysis (TEN), drug reactions with eosinophilia and systemic symptoms (DRESS), and acute generalized exanthematous pustulosis (AGEP).[3] Although SCARs are rare, they can significantly impact patient morbidity and mortality. Allopurinol, a uric-lowering agent used for gout and asymptomatic hyperuricemia, is known to be associated with CADRs.[4,5] The incidence of CADRs has been reported as 0.3–2%. Among patients receiving allopurinol[6,7] In Thailand, the incidences of TEN, DRESS, and SJS from allopurinol were 0.21, 0.53, and 1.39/1,000 persons over 5 years, respectively.[8] The mean onset for allopurinol-induced CADRs among Thai patients was found to be 22.2 days (range, 7–42 days).[9] The mortality rate from SCARs was reported to be 11.39%.[10] Therefore, it is crucial to prevent allopurinol-induced CADRs to reduce the risk and avoid potential consequences.

The reported factors associated with allopurinol-induced SCARs include female, elderly (aged 60 or above), chronic kidney disease (CKD), cardiovascular disease, concomitant use of diuretics, initiating doses of the drug exceeding 100 mg/day, and genetic factors such as HLA-B*58:01.[11-13] The association between this allele and the hypersensitivity reactions could be explained by the pharmacological interaction (p-i) concept. The interaction between allopurinol (or its metabolite oxypurinol) and the HLA-B*58:01 of antigen-presenting cells, triggers a cascade of cytotoxic T lymphocytes-associated immune responses, resulting in skin rash or epidermal detachment.[14]

HLA-B*58:01 prevalence is high in Asian populations, particularly in Taiwanese, Han Chinese, Koreans, and Thais.[11,12] The Thai population with HLA-B*58:01 has a significantly higher risk of developing allopurinol hypersensitivity or allopurinol-induced CADRs (e.g., SJS/TEN, DRESS, and MPE) compared to those without HLA-B*58:01. The odds ratio for developing SJS/TEN is 228.5–579, DRESS is 430.33, and MPE is 144.[9,10,15] The HLA-B*58:01 screening test for the Thai population regarding CADRs associated with allopurinol has a 96.6% sensitivity, 96.0% specificity, 87.88% positive predictive value, and 98.97% negative predictive value.[9]

The HLA-B*58:01 screening test before initiating allopurinol for newly diagnosed gout patients was endorsed by the National Health Security Office on March 15, 2021.[16] However, the test requesting rate was suboptimal since the acceptance level among prescribers was low, and a lack of studies on the impact of the test in preventing CADRs in clinical practice. Consequently, this study aimed to assess (1) the effectiveness of the HLA-B*58:01 screening test before initialing allopurinol to decrease the incidence of allopurinol-induced CADRs (either MCARs or SCARs) and (2) its association with direct medical costs in allopurinol-induced CADRs management at a tertiary hospital.

MATERIALS AND METHODS

This retrospective cohort study protocol was approved by the medical service department Bangkok Institutional Review Board (protocol code U002hh/67_EXP).

Population and Sample

The medical records of patients with gout or asymptomatic hyperuricemia, planning to initiate allopurinol at the Charoenkrung Pracharak Hospital, Bangkok, between January 1, 2019, and December 31, 2023, were reviewed. The inclusion criteria for both groups were being aged 20 or above and diagnosed with gout or asymptomatic hyperuricemia by the physician using ICD-10 codes M10 and E79.0. For the study group, patients also had to have undergone HLA-B58:01 testing before initiating allopurinol or within the 1st month without any adverse drug reaction (ADRs). For the comparison group, patients did not undergo the HLA-B*58:01 screening test. The exclusion criteria were: (1) Patients with a history of allopurinol-induced CADRs, (2) patients who had received allopurinol for more than 1 month, (3) patients who received allopurinol to prevent tumor lysis syndrome, and (4) patients who could not be continuously followed up for 90 days after initiating allopurinol. The patients were divided into two groups: Those who underwent the HLA-B*58:01 test (study group) and those who did not test (comparison group).

The sample size was determined using the G*power program.[17] The reported incidence of allopurinol-induced CADRs was approximately 2%[6,7] which was anticipated to be reduced to 0.2% by the HLA-B*58:01 screening test. Thus, the calculated effect size was 0.129. Chi-square test statistics were selected to be used in data analysis with a confidence level (α) and a test power set at 0.05 (two-sided), and 80%, respectively. This resulted in a total sample size of 476 patients, equally divided into the study group and the comparison group (238 patients in each group).

Outcomes

There were two categories of CADRs; MCARs and SCARs. MCARs included pruritus, urticaria, MPE, and erythema. SCARs included SJS, TEN, and DRESS.[18] The recorded CADRs were evaluated by the trained pharmacist using Naranjo's algorithm (score of possible or above) and confirmed by the physicians or dermatologists. Patients who did not develop any skin reactions within 90 days were defined as patients who tolerated allopurinol.[19,20]

The cumulative incidence of allopurinol-induced CADRs in the study group (% I_{test}) and comparison group (% $I_{no\ test}$) were as follows;

$$\text{Incidence CADRs, \% } I_{test} = \left\{\begin{array}{l}\text{That are Total number of patients who}\\ \text{experienced CADRs. Divided by}\\ \text{(Total number of patients who}\\ \text{tested negative for HLA}\\ \text{B*5801 taking allopurinol plus}\\ \text{who positive for HLA B*58 : 01 test)}\end{array}\right\}\times 100$$

$$\text{Incidence CADRs, \% } I_{no\ test} = \left\{\begin{array}{l}\text{That are Total number of patients who experienced CADRs.}\\ \text{Devided by Patients taking allopurinol no HLA B*58 : 01 test.}\end{array}\right\}\times 100$$

The incidence of allopurinol-induced MCARs and SCARs is using the same calculation method as CADRs.

The direct medical costs associated with allopurinol-induced CADRs management included the cost of HLA-B*58:01 screening (C_1), total costs related to allopurinol-induced CADRs treatment (i.e., physician's fees, physical examination costs,

medication costs, laboratory testing costs, and hospitalization costs) (C_2), cost of allopurinol medication (C_3), and cost of other uric acid-lowering medications (i.e., febuxostat, sulfinpyrazone, probenecid, and benzbromarone) (C_4). These costs were calculated based on the healthcare providers' perspective, over the 90-day follow-up period. The exchange rate was 36.61 Baht to 1 US dollars (USD). The differences in the average direct medical costs associated with allopurinol-induced CADRs management between the groups were equal to the costs of the study group minus the comparison group.

A subgroup analysis to evaluate the association between interested allopurinol-induced CADRs, namely, (1) MPE, (2) erythematous rash, and (3) SCARs and non-genetic risk factors was conducted. Only patients with these reactions or patients without any skin reactions were included in the subgroup analysis using multiple logistic regression.[21] The level of significance was set at a $P < 0.05$.

Data Analysis

The data were analyzed using the statistical package for the social science version 28.0. Patients' characteristics were presented by descriptive statistics. Continuous variables were presented using mean with standard deviation or median with interquartile range (IQR) based on data distribution. To compare between groups, the Chi-square test, independent *t*-tests, or the Mann–Whitney U test were used as appropriate.

RESULTS

Patient Characteristics

A total of 1026 patients were included in this study: 281 patients (27%) and 745 patients (73%) for the study and comparison groups, respectively. In the study group, 25 patients (8.9%) received allopurinol not more than 1 month before the test while others started allopurinol after knowing the test result. Positive tests were found in 53 patients (19% of the study group). Among these positive HLA-B*58:01 patients, 34 patients received other alternative uric acid-lowering medications while the rest did not receive any medications but used non-pharmacologic treatments instead. Among the patients with negative results, 163 individuals received allopurinol. Sixty-five patients with negative results also used non-pharmacologic treatment. All patients in the comparison group were treated with allopurinol [Figure 1].

The baseline characteristics of the study and comparison groups were mostly similar. However, significant differences were found in age, gender, Stage 3 or higher CKD, indications for medication, and initiating dose of allopurinol [Tables 1 and 2].

Allopurinol-induced CADRs

There were 47 cases of allopurinol-induced CADRs in this study. In the study group, SCARs were not found, and there were simply three cases of MCARs. The patient who tested positive for HLA-B*58:01 experienced a pruritic rash, while two patients who tested negative had a pruritic rash and an oral ulcer. The median onset of MCARs was 29 (21.5–58) days. The comparison group had 44 cases of CADRs (MCARs = 37, SCARs = 7). Among the 37 cases of MCARs, there were nine pruritic rashes, eight MPE, six erythematous rashes, six oral ulcers, two with fever and myalgia along with oral ulcer, two with lip rash, and one case each of angioedema, urticaria, bullous eruption, and fixed drug eruption. The median onset of MCARs was 20 (13–30) days, with a median hospital stay of 4 days. Seven cases were reported SCARs, including four cases of SJS,

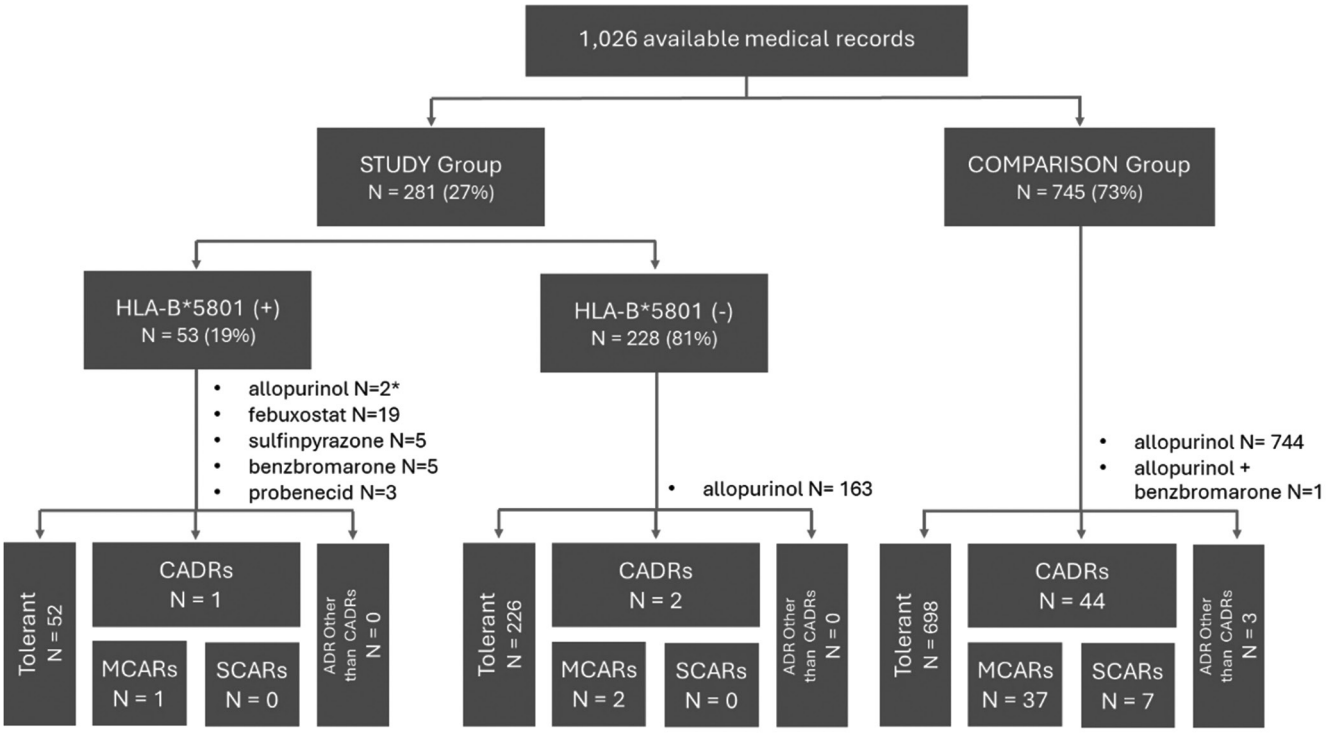

Figure 1: HLA-B*5801 screening test and outcomes. CADRs: Cutaneous adverse drug reactions, MCARs: Mild cutaneous adverse drug reactions, SCARs: Severe cutaneous adverse drug reactions, *two cases that received allopurinol before the test

Table 1: Patient characteristics

Patient characteristics	Study group				Comparison group	*P*-value*
	HLA-B*58:01 positive *n*=53	HLA-B*58:01 negative *n*=228	*P*-value+	Total *n*=281	Total *n*=745	
1. Mean age, years (SD)	71.77 (10.80)	66.76 (12.56)	0.198	67.68 (12.38)	61.56 (13.92)	<0.001
2. Sex (%)						
Male	36 (67.9)	146 (64)	0.593	182 (64.8)	574 (77)	<0.001
Female	17 (32.1)	82 (36)		99 (35.2)	171 (23)	
3. Median BMI, kg/m^2, (IQR)	24.69 (21.54–26.50)	24.22 (21.68–28.42)	0.308	24.34 (21.62–27.55)	25.39 (22.21–29.30)	0.009
4. Smoking (%)	5 (9.4)	20 (8.8)	1.000	25 (8.9)	77 (10.3)	0.492
5. Alcohol drinking (%)	12 (5.3)	4 (7.5)	0.744	16 (5.7)	56 (7.5)	0.308
6. Underlying disease (%)						
Hypertension	43 (81.1)	183 (80.3)	0.886	226 (80.4)	510 (68.5)	<0.001
Dyslipidemia	36 (67.9)	152 (66.7)	0.861	188 (66.9)	494 (66.3)	0.857
Diabetes mellitus	25 (47.2)	91 (39.9)	0.334	116 (41.3)	226 (30.3)	<0.001
Stroke	8 (15.1)	12 (5.3)	0.019	20 (7.1)	44 (5.9)	0.474
Rheumatism	0 (0)	1 (0.4)	1.000	1 (0.4)	3 (0.4)	1.000
Chronic Kidney Disease, CKD	41 (77.4)	178 (78.1)	0.910	219 (77.9)	357 (47.9)	<0.001
+CKD Stage 3 (CrCl 30 - 59 mL/min/m^2)	21 (39.6)	88 (38.6)	0.890	109 (38.8)	244 (32.8)	0.069
+CKD Stage 4 (CrCl 15 - 29 mL/min/m^2)	16 (30.2)	73 (32)	0.797	89 (31.7)	98 (13.2)	<0.001
+CKD Stage 5 (CrCl <15 mL/min/m^2)	4 (7.5)	17 (7.5)	1.000	21 (7.5)	15 (2)	<0.001
Ischemic heart disease	8 (15.1)	21 (9.2)	0.205	29 (10.3)	111 (14.9)	0.057
Chronic heart failure	0 (0)	15 (6.6)	0.083	15 (5.3)	26 (3.5)	0.178
Cancers	3 (5.7)	6 (2.6)	0.378	9 (3.2)	14 (1.9)	0.202
Others	16 (30.2)	62 (27.2)	0.661	78 (27.8)	187 (25.1)	0.386
7. Adverse drug reactions history (%)						
Side effect	5 (9.4)	7 (3.1)	0.054	12 (4.3)	34 (4.6)	0.840
Drug hypersensitivity	5 (9.4)	33 (14.5)	0.334	38 (13.5)	72 (9.7)	0.075
8. Herbal/supplement use (%)	0 (0)	6 (2.6)	0.365	6 (2.1)	22 (3)	0.473
9. Diuretic use (%)						
Hydrochlorothiazide	0 (0)	2 (0.9)	1.000	2 (0.7)	15 (2)	0.178
Furosemide	7 (13.2)	40 (17.5)	0.446	47 (16.7)	110 (14.8)	0.437
10. Indication (%)						
Asymptomatic hyperuricemia	23 (43.4)	121 (53.1)	0.204	144 (51.2)	263 (35.3)	<0.001
Gout	30 (56.6)	107 (46.9)		137 (48.8)	482 (64.7)	

+Compare between HLA-B*58:01 (+) and HLA-B*58:01 (–) groups, *Compare between study and comparison groups, Statistic significance $P<0.05$. CKD: Chronic kidney disease, CrCl: Creatinine clearance (Cockcroft-Gault Equation)

Table 2: Initiating dose of allopurinol in the study group and comparison group

Initiating dose of allopurinol	Study group				Comparison group	*P*-value*
	HLA-B*58:01 Positive *n*=2	HLA-B*58:01 Negative *n*=163	*P*-value+	Total *n*=165	Total *n*=745	
The median initiating dose of allopurinol, mg/day (IQR)	50 (50)	50 (50–100)	0.265	50 (50–100)	100 (50–100)	<0.001

+Compare between HLA-B*58:01 (+) and HLA-B*58:01 (–) groups, *Compare between study and comparison groups, statistical significance $P<0.05$

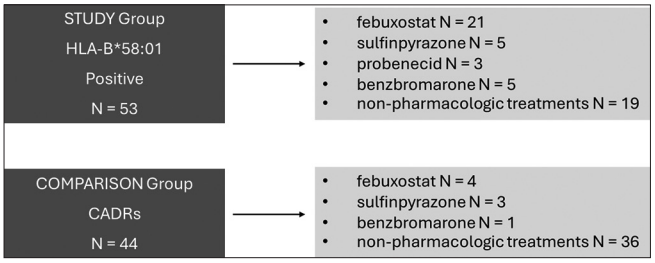

Figure 2: Alternative regimen

one case of SJS with DRESS, one case of SJS overlap TEN with DRESS, and one case of DRESS. The median onset of SCARs was 25 (14–41) days, with a median hospital stay of 8 (4–26) days. During the SCARs management, One SJS case required a critical care unit for 21 days, and only one case was diagnosed with SJS overlap TEN with DRESS had been done HLA-B*58:01 testing revealed a positive result. In SCARs, there were many complications; stomatitis (n = 6, 86%), genital ulcer (n = 1, 14%), one organ involvement (n = 3, 43%), and more than one organ involvement (n = 1, 14%) were found. One patient died due to ventilator-associated pneumonia, with a mortality of 14.3%. Even though there were three cases of unrelated CADRs, 2 with fever and one with transaminitis [Supplements 1 and 2].

Alternative Regimen

In this study, 34 out of 53 patients who tested positive for HLA-B*58:01 received alternative drugs. Twenty-one cases with febuxostat, of which two individuals who had allopurinol before and then had positive results were switched to febuxostat. Five cases with sulfinpyrazone, three cases with probenecid, and five cases with benzbromarone. Eight out of 44 patients with allopurinol hypersensitivity in the comparison group received alternative drugs: Four patients with febuxostat, three patients with sulfinpyrazone, and one patient with benzbromarone [Figure 2].

Incidence of Allopurinol-induced CADRs

During the 90-day monitoring period, ADRs were observed in two groups. In the study group, 163 patients who tested negative for HLA-B*58:01 received treatment with allopurinol, and 53 patients who tested positive for HLA-B*58:01 showed an incidence of CADRs at 1.4% (n = 3). In the comparison group of 745 patients, the incidence of CADRs was higher at 5.9% (n = 44) (P = 0.007). The incidence of MCARs was 1.4% (n = 3) in the study group, while the incidence of MCARs in the comparison group was higher at 5.0% (n = 37) (P = 0.02). No SCARs were observed in the study group, while the comparison group had a SCARs incidence of 0.9% (P = 0.216) [Table 3].

Non-genetic Risk Factors for Allopurinol-induced CADRs

In the subgroup data, the median doses of allopurinol in patients with (n = 21) and without CADRs (n = 860) were 100 mg (IQR: 100–300) and 100 mg (IQR: 50–100), respectively. To investigate the potential non-genetic risk factors for the development of allopurinol-induced CADRs, we applied a binary logistic regression model, in which the following factors were included: (1) sex, (2) aged 60 or above, (3) CKD, (4) ischemic heart disease, (5) chronic heart failure, (6) hydrochlorothiazide use, (7) furosemide use, and (8) initiating allopurinol dose exceeding 100 mg/day.[11] Through logistic regression analysis, only an initiating dose of allopurinol exceeding 100 mg/day was statistically associated with an increased risk of CADRs with the odds ratio 6.68 (P < 0.001) [Table 4].

Direct Medical Costs of Allopurinol-induced CADRs Management

The mean difference in direct medical treatment costs in 90 days associated with allopurinol-induced CADRs management between groups was (1) Cost of HLA-B*58:01 testing (C1): 27.22 USD per person. (2) Cost of CADRs management (C2): 2,190.69 USD per person. (3) Allopurinol medication cost (C3): 0.39 USD per person. (4) Alternative uric acid-lowering medications cost (C4): 35.43 USD per person. Therefore, the average total costs between the study and the comparison groups were 177.33 USD and 2,305.76 USD per person, respectively. The average cost difference was 2,128.43 USD per person [Table 5].

DISCUSSION

In this study, the prevalence of HLA-B*58:01 was 19%, corresponding to the prevalence of HLA-B*58:01 in the Thai population, which ranges from 7.7 to 16.33%.[22,23] Recommendations from the American College of Rheumatology (ACR) in 2020 suggested that screening in populations with a high prevalence of HLA-B*58:01, such as Han Chinese, Koreans, Thais, and African Americans, recommended before initiating allopurinol. The prevalence of this study and ACR could warrant the use of HLA-B*58:01 screening test before initiating allopurinol in clinical practice.

The incidence of MCARs in the study group was less than that in the comparison group, with a significant difference. In contrast, the incidences of SCARs among the two groups were not statistically significantly different. However, it was clinically meaningful and consistent with the study's findings by Ko *et al*.,[24] Jung *et al*.,[19] Park *et al*.,[20] and Wong *et al*.[25]

Table 3: Incidence outcome between study and comparison groups

Incidence	Study group				Comparison group	*P*-value*
	HLA-B*58:01 positive *n*=53 (%)	HLA-B*58:01 negative *n*=163 (%)	*P*-value+	Total *n*=216 (%)	*n*=745 (%)	
CADRs	1 (1.9)	2 (1.2)	1.000	3 (1.4)	44 (5.9)	0.007
MCARS	1 (1.9)	2 (1.2)	1.000	3 (1.4)	37 (5.0)	0.02
SCARs	0 (0)	0 (0)	-	0 (0)	7 (0.9)	0.216

+Compare between HLA-B*58:01 positive and negative in the study group, *Compare between the study group and comparison group, statistical significance $P<0.05$, CADRs: Cutaneous adverse drug reactions, MCARs: Mild cutaneous adverse drug reactions, SCARs: Severe cutaneous adverse drug reactions

Table 4: Logistic regression analysis for non-genetic risk factors of allopurinol-induced CADRs

Variables	B	Odds ratio	95% CI	*P*-value
1. Gender, female	−0.222	0.801	(0.246–2.611)	0.713
2. Aged 60 or above	−0.266	0.766	(0.255–2.300)	0.635
3. Chronic kidney disease	0.735	2.086	(0.658–6.612)	0.212
4. Ischemic heart disease	0.514	1.672	(0.481–5.814)	0.418
5. Chronic heart failure	0.093	1.098	(0.129–9.346)	0.932
6. Hydrochlorothiazide use	−17.673	0.000	(0.000)	0.999
7. Furosemide use	0.088	1.092	(0.300–3.973)	0.894
8. Initiating allopurinol dose exceeding 100 mg/day	1.899	6.682	(2.476–18.033)	<0.001
Constant	−4.390			

Allopurinol-induced CADRs, including erythematous rash ($n=6$), MPE ($n=8$), SCARs ($n=7$), and control ($n=860$) who tolerated allopurinol use in 90 days, statistical significance $P<0.05$

Table 5: The direct medical costs associated with allopurinol-induced CADRs management in 90 days

The average direct medical costs, USD per person	Study group, C_{Test}	Comparison group, $C_{No\ test}$	ΔDifference cost*
1. Average cost of HLA-B*58:01 testing; C_1	27.22	0	27.22
2. Average cost of CADRs management; C_2			
Cost of MCARs management	0.17	3.23	−3.06
Cost of SCARs management	0	2,187.63	−2,187.63
3. Average cost of allopurinol; C_3	2.01	2.40	−0.39
4. Average cost of alternative drugs; C_4	147.93	112.50	35.43
Total	177.33	2,305.76	−2,128.43

The exchange rate was 36.61 Baht=1 US dollars (USD), and the *sign "negative" means cost savings

The results of this study demonstrated an effective decrease in the overall incidence of CADRs. However, previous studies have shown that the relation between the HLA-B*58:01 gene and CADRs manifestations was only seen in MPE, SJS/TEN, and DRESS. Other skin reactions such as rash, itching, erythematous rash, MPE, pruritus, urticaria, and AGEP can still occur even if the HLA-B*58:01 gene is negative. The benefit of the HLA-B*58:01 screening test for mild reactions in clinical practice was problematic. This study explained that the HLA-B*58:01 test decreased the overall incidence of CADRs during a 90-day follow-up period. It cannot be definitively stated that patients will refrain from all skin reactions of allopurinol hypersensitivity, even if HLA-B*58:01 is negative.

This study found that the median onset of allopurinol-induced CADRs was 20–29 days. This is similar to the findings of a study in Thailand by Sukasem *et al*.,[9] which reported an average onset of allopurinol-induced CADRs at 22 days. This suggests that developing CADRs to allopurinol requires a certain period of time. Therefore, this study screening be conducted either before or within the 1st month of allopurinol initiation without ADRs.

The study found that the direct medical costs for allopurinol-induced CADRs management were fewer in the study group compared to the comparison group during the 90-day follow-up period, especially in the cost of SCARs management. These results suggested that the cost of genetic testing was more valuable than the SCARs treatment and confirmed with previous cost-effectiveness research in Thailand conducted by Saokaew *et al*.[26]

The characteristics of patients that might influence allopurinol-induced CADRs include being predominantly male, aged 60 years or above, and around half of the patients with a history of CKD Stage 3 or higher (CrCl <60 mL/min/m^2). Moreover, the initiating dose of allopurinol in the study group was lower than the comparison group. A subgroup analysis

of the patients who experienced allopurinol-induced CADRs was associated with the initiating allopurinol dose exceeding 100 mg/day. This result aligns with previous research conducted by Yang *et al*.[11] and Stamp *et al*.[27] The 2020 ACR recommendations using a low initiating dose of allopurinol (<100 mg/day, and lower in CKD).

According to the guidelines of the Clinical Pharmacogenetics Implementation Consortium,[28] if patients test positive for the HLA-B*58:01 gene, the use of allopurinol is not recommended unless necessary. Alternative medications, such as febuxostat, should be considered. This study presented real clinical data that concordance with these guidelines; HLA-B*58:01 tested positive, and physicians prescribed alternative uric acid-lowering medications, such as febuxostat, sulfinpyrazone, benzbromarone, or probenecid.

The limitations of this study were: (1) In the comparison group, most allopurinol hypersensitivities were not confirmed by HLA-B*58:01 testing, making it difficult to conclude the influence of the HLA-B*58:01 genetic factor on allopurinol-induced CADRs. (2) Other confounding factors were not controlled due to the small number of patients with allopurinol-induced CADRs. (3) The study lacked a follow-up period, which was only 90 days. (4) This study only includes direct medical costs within 90 days.

To improve patient care and clinical practices, we suggest conducting further research on more extensive, other genetics that can impact allopurinol-induced CADRs and diverse populations across multiple centers, including hospitals with different HLA-B*58:01 screening policies.

CONCLUSION

This screening of HLA-B*58:01 could effectively prevent allopurinol-induced CADRs and cost-effectiveness. Therefore, it is recommended that HLA-B*58:01 screening be conducted either before or within the 1st month of allopurinol initiation among Thai patients with gout or hyperuricemia. In addition, the initial daily dose of allopurinol should not exceed 100 mg. Intensive monitoring for signs or symptoms of CADRs is warranted for at least 90 days after treatment initiation. Implementing these measures could significantly enhance patient safety and therapeutic outcomes, underscoring the importance of personalized medicine in clinical practice.

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CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest.

REFERENCES

1. Riedl MA, Casillas AM. Adverse drug reactions: Types and treatment options. Am Fam Physician 2003;68:1781-90.
2. Palapinyo S, Klaewsongkram J, Mongkolpathumrat P, Leelakanok N, Yotsombut K. A multidisciplinary approach to verify and de-label of drug allergic histories in a university hospital in Thailand: A retrospective descriptive study. J Pharm Policy Pract 2023;16:12.
3. Mockenhaupt M. Epidemiology of cutaneous adverse drug reactions. Chem Immunol Allergy 2012;97:1-17.
4. Thai Rheumatism Association. Guideline for Management of Gout. Bangkok: Thai Rheumatism Association; 2012.
5. FitzGerald JD, Dalbeth N, Mikuls T, Brignardello-Petersen R, Guyatt G, Abeles AM, *et al*. 2020 American college of rheumatology guideline for the management of gout. Arthritis Care Res (Hoboken) 2020;72:744-60.
6. Pharmacogenomics for Rational Drug Use (RDU) in Thailand. Clinical Practice Guidelines for HLA-B*58:01 Genetic Testing to Guide the Use of Allopurinol, Revised Edition 2021: Faculty of Pharmacy, Mahidol University; 2021. p. 17.
7. Excess of ampicillin rashes associated with allopurinol or hyperuricemia. A report from the Boston collaborative drug surveillance program, Boston University medical center. N Engl J Med 1972;286:505-7.
8. Limkobpaiboon S, Na Ayudhya DP, Dhana N, Jongjarearnprasert K. Prevalence and mortality rate of severe cutaneous adverse reactions in Siriraj hospital. Chulalongkorn Med J 2010;54:467-78.
9. Sukasem C, Jantararoungtong T, Kuntawong P, Puangpetch A, Koomdee N, Satapornpong P, *et al*. HLA-B (*) 58:01 for allopurinol-induced cutaneous adverse drug reactions: Implication for clinical interpretation in Thailand. Front Pharmacol 2016;7:186.
10. Saksit N, Tassaneeyakul W, Nakkam N, Konyoung P, Khunarkornsiri U, Chumworathayi P, *et al*. Risk factors of allopurinol-induced severe cutaneous adverse reactions in a Thai population. Pharmacogenet Genomics 2017;27:255-63.
11. Yang CY, Chen CH, Deng ST, Huang CS, Lin YJ, Chen YJ, *et al*. Allopurinol use and risk of fatal hypersensitivity reactions: A nationwide population-based study in Taiwan. JAMA Intern Med 2015;175:1550-7.
12. Hung SI, Chung WH, Liou LB, Chu CC, Lin M, Huang HP, *et al*. HLA-B*5801 allele as a genetic marker for severe cutaneous adverse reactions caused by allopurinol. Proc Natl Acad Sci U S A 2005;102:4134-9.
13. Do MD, Mai TP, Do AD, Nguyen QD, Le NH, Le LG, *et al*. Risk factors for cutaneous reactions to allopurinol in Kinh Vietnamese: Results from a case-control study. Arthritis Res Ther 2020;22:182.
14. Wang CW, Dao RL, Chung WH. Immunopathogenesis and risk factors for allopurinol severe cutaneous adverse reactions. Curr Opin Allergy Clin Immunol 2016;16:339-45.
15. Tassaneeyakul W, Jantararoungtong T, Chen P, Lin PY, Tiamkao S, Khunarkornsiri U, *et al*. Strong association between HLA-B*5801 and allopurinol-induced Stevens-Johnson syndrome and toxic epidermal necrolysis in a Thai population. Pharmacogenet Genomics. 2009;19:704-9.
16. Announcement of the National Health Security Committee. Subjective: Categories and Scope of Public Health Service 2021. Vol. 138 Special Issue 98. Royal Thai Government Gazette; 2021. p. 19.
17. Faul F, Erdfelder E, Buchner A, Lang AG. Statistical power analyses using G*Power 3.1: Tests for correlation and regression analyses. Behav Res Methods 2009;41:1149-60.
18. Greenwood Village(CO): IBM Corpration. Allopurinol. In: Depth Answers; 2022. Available from: https://www.micromedexsolutions.com.subscription required to view [Last accessed on 2022 Aug 19].
19. Jung JW, Kim DK, Park HW, Oh KH, Joo KW, Kim YS, *et al*. An effective strategy to prevent allopurinol-induced hypersensitivity by HLA typing. Genet Med 2015;17:807-14.
20. Park HW, Kim DK, Kim SH, Kim S, Chae DW, Yang MS, *et al*. Efficacy of the HLA-B(*)58:01 screening test in preventing allopurinol-induced severe cutaneous adverse reactions in patients with chronic renal insufficiency-a prospective study. J Allergy Clin Immunol Pract 2019;7:1271-6.
21. Katz MH. Multivariable Analysis: A Practical Guide for Clinicians

and Public Health Researchers. Cambridge: Cambridge University Press; 2011.
22. Yu KH, Yu CY, Fang YF. Diagnostic utility of HLA-B*5801 screening in severe allopurinol hypersensitivity syndrome: An updated systematic review and meta-analysis. Int J Rheum Dis 2017;20:1057-71.
23. Chung WH, Chang WC, Stocker SL, Juo CG, Graham GG, Lee MH, *et al*. Insights into the poor prognosis of allopurinol-induced severe cutaneous adverse reactions: The impact of renal insufficiency, high plasma levels of oxypurinol and granulysin. Ann Rheum Dis 2015;74:2157-64.
24. Ko TM, Tsai CY, Chen SY, Chen KS, Yu KH, Chu CS, *et al*. Use of HLA-B* 58: 01 genotyping to prevent allopurinol induced severe cutaneous adverse reactions in Taiwan: National prospective cohort study. BMJ 2015;351:h4848.
25. Wong CS, Yeung CK, Chan CY, Yap DY, Tang SC, Cheung BM, *et al*. HLA-B*58:01 screening to prevent allopurinol-induced severe cutaneous adverse reactions in Chinese patients with chronic kidney disease. Arch Dermatol Res 2022;314:651-9.
26. Saokaew S, Tassaneeyakul W, Maenthaisong R, Chaiyakunapruk N. Cost-effectiveness analysis of HLA-B*5801 testing in preventing allopurinol-induced SJS/TEN in Thai population. PLoS One 2014;9:e94294.
27. Stamp LK, Taylor WJ, Jones PB, Dockerty JL, Drake J, Frampton C, *et al*. Starting dose is a risk factor for allopurinol hypersensitivity syndrome: A proposed safe starting dose of allopurinol. Arthritis Rheum 2012;64:2529-36.
28. Saito Y, Stamp LK, Caudle KE, Hershfield MS, McDonagh EM, Callaghan JT, *et al*. Clinical pharmacogenetics implementation consortium (cpic) guidelines for human leukocyte antigen B (HLA-B) genotype and allopurinol dosing: 2015 update. Clin Pharmacol Ther 2016;99:36-7.

Supplementary Materials

Supplement 1: Patients of allopurinol-induced CADRs in the study and comparison groups

Types of allopurinol-induced CADRs	Study group			Comparison group *n*=44
	HLA-B*58:01 positive	HLA-B*58:01 negative	Total *n*=3	
Mild cutaneous adverse drug reactions (MCARs)	**1**	**2**	**3**	**37**
Prurutic rash	1	1	2	9
MPE	0	0	0	8
Erythematous rash	0	0	0	6
Oral ulcer	0	1	1	6
Fever myalgia and oral ulcer	0	0	0	2
Lip rash	0	0	0	2
Angioedema	0	0	0	1
Urticaria	0	0	0	1
Bullous eruption	0	0	0	1
Fixed drug eruption	0	0	0	1
Severe cutaneous adverse drug reactions (SCARs)	**0**	**0**	**0**	**7**
SJS	0	0	0	4
SJS with DRESS	0	0	0	1
SJS overlaps TEN with DRESS	0	0	0	1
DRESS	0	0	0	1
Others, excluding cutaneous adverse reactions	**0**	**0**	**0**	**3**
Fever	0	0	0	2
Transaminitis	0	0	0	1

Supplement 2: Characteristics of patients with allopurinol-induced SCARs

Patients	Years	Age	Sex	Allopurinol dosing (mg/day)	CrCl <60 ml/min/m²	Onsets of reaction, days	HLA-B* 58:01 test	Clinical appearance	ALDREN's score	RegiSCAR's score
1	2019	79	F	50	(+)	14	0	SJS	Probable	-
2	2019	70	M	300	(-)	56	0	SJS	Probable	-
3	2020	58	M	50	(+)	41	0	SJS	Probable	-
4	2020	21	M	300	(-)	25	0	DRESS	-	Possible
5	2020	43	M	100	(-)	38	0	SJS with DRESS	Probable	Probable
6	2020	56	M	600	(-)	7	0	SJS	Probable	-
7	2021	69	M	100	(+)	19	(+)	SJS overlap TEN with DRESS	Probable	Probable

Patients	SCORTEN (%)	Naranjo's score	Mucosal involvement	Internal organ involvement	Others cause	Hospitalization, days	ICU, days	Treatment	Outcome	Co-medication use
1	58.3	Probable	(+) Stomatitis	(%) Elevated atypical lymphocyte	(-) H/C, (-) HAV/HBV/HCV	26	21	0, 1, 5	Death*	-
2	3.2	Probable	(+) Stomatitis, (+) Genital ulcer	-	-	8	0	0, 1, 5	Recovery	-
3	12.1	Probable	(+) Stomatitis	-	(-) H/C	3	0	0, 1, 2, 5	Recovery	-
4	-	Possible	(-)	(+) Eosinophilia, (%) Elevated atypical lymphocyte	-	4	0	0, 1, 2, 5	Recovery	Colchicine
5	3.2	Probable	(+) Stomatitis	(+) Liver failure, (+) Eosinophilia, (%) Elevated atypical lymphocyte	(-) HBV/HCV	10	0	0, 1, 2, 5	Recovery	-
6	3.2	Probable	(+) Stomatitis	(+) Liver failure	(-) H/C	6	0	0, 1, 2, 5	Recovery	-
7	58.3	Probable	(+) Stomatitis	(+) Liver failure, (+) Renal failure, (+) CPK increase, (+) Eosinophilia	(-) H/C, (-) HAV/HBV/HCV	35	0	0, 1, 2, 3, 5	Recovery	-

CKD: Chronic kidney disease, Creatinine Clearance (Cockcroft-Gault Equation); CrCl<60 ml/min/m², HLA-B*58:01; 0=not test, Treatment; hold only=0, antihistamines=1, systemic corticosteroids=2, IVIG=3, cyclosporin=4, others=5, *Death=Due to VAP, VAP=Ventilator-associated pneumonia, H/C: Hemoculture, HAV: Hepatitis A virus, HBV: Hepatitis B virus, HCV: Hepatitis C virus