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ORIGINAL PAPER

HLA-B*58:01 screening to prevent allopurinol-induced severe cutaneous adverse reactions in Chinese patients with chronic kidney disease

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Abstract

Human leukocyte antigen (HLA)-B*58:01 allele is a significant risk factor for allopurinol-induced severe cutaneous adverse reactions (SCARs) which is potentially fatal. In some studies, chronic kidney disease (CKD) was also implicated to compound the risk of SCARs. We aim to investigate if pre-treatment HLA-B*58:01 screening can prevent allopurinol-induced SCARs in Chinese patients with CKD and its cost-effectiveness. We prospectively recruited Chinese CKD patients who required allopurinol during 2011–2015 and performed pre-treatment HLA testing (HLA screening group). Patients tested positive for HLA-B*58:01 were refrained from allopurinol while those tested negative were prescribed allopurinol. The incidence of SCARs in the HLA screening group was compared with the historical control in previous 5 years and the cost-effectiveness of HLA testing was analyzed. In the historical control (2006–2010), 3605 patients on allopurinol were screened, 22 out of 1027 (2.14%) CKD Chinese patients newly started on allopurinol developed SCARs, including 6 SJS/TEN. In the HLA screening group, 28 out of 192 patients (14.6%) tested HLA-B*58:01 positive were advised to avoid allopurinol; 156 out of 164 HLA-B*58:01-negative patients received allopurinol and none developed SCARs. The incidence rate of SCARs was significantly lower in the HLA screening group compared with controls (0% vs 2.14% respectively, $p=0.037$*). The targeted HLA screening approach was associated with lower healthcare costs compared with no HLA screening (US$ 92,430 vs US$ 281,226). Pre-treatment HLA-B*58:01 screening is cost-effective to target on patients with CKD in Chinese to prevent allopurinol-induced SCARs.

Keywords Allopurinol · HLA-B*58:01 · Chronic kidney disease · SCARs · SJS · TEN

Introduction

Steven–Johnson syndrome (SJS) and its related disease, toxic epidermal necrolysis (TEN) represent severe cutaneous adverse reactions (SCARs) that are potentially fatal. Withdrawal of the potential culprit drugs is by far the best approach to improve the outcome of patients with SJS/TEN.

Risk factors for SCARs are multi-factorial and genetic susceptibility such as human leucocyte antigen (HLA) specific allele, is one of the most important factors. Whether a patient will develop drug-induced SCARs is highly influenced by the expression of HLA. HLA are antigen presenting proteins on cell surfaces that are responsible for immune system regulation and are involved in the pathogenesis of drug hypersensitivity reactions [1]. Patients carrying the HLA-B*58:01 allele and received allopurinol were associated with 80-fold risk of development SJS/TEN compared

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with those without the allele [2]. A local study in Hong Kong also reported that allopurinol-induced SCARs patients carried at least one HLA-B*58:01 allele; however, there were also tolerant patients who carried the HLA-B*58:01 allele without developing the adverse reaction [3, 4].

HLA allele screening represents an important means to prevent drug-induced SCARs [1, 5]. In this context, the implementation of mandatory HLA allele screening prior to use of an anti-convulsant-carbamazepine in all public hospitals in Hong Kong since 2008 has helped to reduce incidence of carbamazepine-related SCARs and SJS/TEN [6, 7]. Theoretically, a similar approach can be adopted to minimize the risk of SCARs and SJS/TEN in patients who were to be commenced on allopurinol. However, one should recognize that the highest prevalence of HLA-B*15:02 allele was up to 20% in China and some Asian populations [6] and the odds ratio (OR) of developing of SJS/TEN in allele carrier was over 2500 compared to carbamazepine-tolerant patient without the allele [7]. The prevalence of HLA-B*58:01 varies from 8 to 20% in Chinese population [6–9] and the overall incidence of SJS/TEN is less common, thus the cost-effectiveness of screening HLA alleles in all patients who were to start allopurinol treatment remains undefined. It is postulated that such approach may be more cost-effective in high-risk patients, such as those with pre-existing CKD. Based on these backgrounds, this prospective study was set forth to investigate whether HLA screening can help prevent allopurinol-induced SCARs in CKD patients and the cost-effectiveness of this approach.

Materials and methods

Patients

This study was approved by the Institutional Review Board of the University of Hong Kong and Hospital authority, Hong Kong West Cluster (IRB: UW11-350). The study was conducted in full compliance with the ICH E6 guideline for Good Clinical Practice (ICH-GCP) and the principles of the Declaration of Helsinki. All subjects aged 18 years of age or above, attending Renal Clinics of two major tertiary hospitals in Hong Kong who have been diagnosed with CKD (including those with kidney transplantation) were screened. We defined chronic kidney disease based on the presence of either known kidney damage (including those with kidney transplantation) or presence of decreased kidney function (glomerular filtration rate (GFR) < 60 ml/min/1.73cm^2) for 3 or more months [10]. We prospectively recruited patients who have not previously received allopurinol and who would normally have received it at the time of screening. The exclusion criteria were: (1) patients who were not ethnic Han Chinese; (2) patients who had previous haematopoietic stem cell transplantation; (3) patients with history of blood transfusion; and (4) patients with a documented history of allergic adverse reaction to allopurinol. We compared the clinical data and outcomes of our recruited patients with historical controls. Retrospective data as historical controls were collected from the hospital electronic patient records (ePR) and clinical data analysis and reporting system (CDARS) [11] in the same hospitals in previous years (2006–2010) to identify CKD patients with a diagnosis of allopurinol-induced SJS, TEN or major skin reactions secondary to drugs by International Classification of Disease, 9th revision, clinical modification (ICD-9-CM) code 695.1 and related conditions including 695.13 (SJS), 695.14 (SJS/TEN overlap), 695.15 (TEN). Diagnoses were confirmed based on clinical records, blood tests and skin biopsy results reviewed by qualified dermatologists.

Study procedures and follow-up

All recruited subjects were prescribed allopurinol at the time of screening visit, but were asked to defer taking the drug until they were informed of their HLA typing results. The results were reported to the clinicians in-charge within 1 week. Patients tested positive for HLA-B*58:01 were advised to refrain from allopurinol and given an alternative medication (febuxostat); whereas those tested negative were advised to commence allopurinol. Demographic and clinical data including age, gender, ethnicity, co-morbidities, allopurinol dosage, renal function, serum urate level at time of screening were documented. We followed up all subjects for at least first 2 months after drug initiation to monitor any symptoms of adverse reactions in regular visit and phone interview, with reference of one local study that the duration of exposure before symptom onset of SCARs ranged 10–56 days with mean 31.2 ± 15.4 [3]. Subjects were assessed by qualified dermatologist(s) immediately in the event that early symptoms of any cutaneous adverse reactions developed.

Genotyping of HLA

EDTA blood sample was collected from each subject. HLA-B*58:01 genotyping was conducted by the Division of Transplantation and Immunogenetics, Queen Mary Hospital, Hong Kong. Genomic DNA from EDTA blood samples was extracted using TBG EZbead blood DNA Extraction Kit (Texas BioGene Inc., Taiwan) according to the manufacturer's instructions. HLA-B genotypes were obtained using polymerase chain-reaction sequence-specific oligonucleotide probe methods using LifeCodes HLA-SSO Typing Kit (Gen-Probe, Stamford, CT) analysed by Luminex 200™ system (Luminex Corp., Austin, TX). HLA-B*58:01 positive was confirmed using sequence-specific primer or

sequence based typing methods utilising the specific primers of SBTexcellerator® HLA typing Kit (Genome Diagnostics, Utrecht, the Netherlands).

Assessment of SCARs including SJS/TEN

The diagnosis of allopurinol-related drug eruption was then confirmed by qualified dermatologists based on clinical presentation with or without histological findings. The diagnostic criteria of severe cutaneous adverse reactions (SCARs), including erythema multiforme major (EMM), SJS and TEN, and drug hypersensitivity syndrome (DHS)/drug reactions with eosinophilia and systemic symptoms (DRESS) are based on the clinical morphology defined by Roujeau [12, 13]. We defined SJS as skin detachment of 10% of body-surface area, overlap SJS/TEN as skin detachment of 10–30%, and TEN as 30%. The criteria for drug hypersensitivity or DRESS are new onset of rash plus two of the following symptoms: eosinophilia, atypical circulating lymphocytes, leucocytosis, acute hepatocellular injury or worsening of renal function [14–16]. For those who did not fall into the above categories, morphological description and percentage of skin involvement were documented clearly by the attending dermatologist.

Identification of culprit drug

Culprit drug was identified based on the guideline, ALDEN (algorithm for assessment of drug causality in SJS/TEN) for identifying the causal medication [17]. Duration of latency was defined from the date of drug initiation to the date of symptoms onset.

Study outcomes and statistical analysis

The primary outcome was the incidence of allopurinol-induced SCARs. The secondary outcomes were allopurinol-induced SJS/TEN and cost-effectiveness of HLA screening approach. The sample size calculation was based on local prevalence of HLA-B*58:01 and study feasibility. With a prevalence of HLA-B*58:01 being 15% locally, ranging from 8 to 20% [2, 3, 6] in Han Chinese and the incidence of allopurinol-induced SCARs in CKD patients was 18% [18, 19], the estimated incidence of allopurinol-induced SCARs in HLA-B*58:01 CKD patients will be 2.7% (0.15 × 0.18). Therefore, 148 patients would achieve 80% power (alpha 0.05, with study: control enrolment ratio 1:3) to detect a reduction in the incidence rate from 2.7% to 0.03%. Categorical variables were expressed as frequencies (percentages), and analysed with Fisher's exact or chi square test where appropriate. Continuous variables were expressed as mean (SD) or median (range), and analysed with independent *t* test or Mann–Whitney tests where appropriate. All statistical analyses were performed using SPSS (version 23.0, SPSS Inc. Chicago, IL, USA). All *p* values were two tailed and *p* value of <0.05 is considered as statistical significance.

Cost of HLA B*58:01 genotyping and hospitalization

The cost of genotyping HLA-B*58:01 in all patients prior to allopurinol commencement were compared with the cost of managing patients who developed SCARs. The cost of genotyping HLA-B*58:01 in all patients prior to allopurinol treatment was calculated as the nominal cost of genotyping HLA-B*58:01 per patients (US$ 90 per patient) multiplied by the total number of patients. The cost of managing patients who developed SCARs was calculated as the daily cost of hospitalization (US$ 3128 per day for intensive/high-dependency units and US$ 654 per day for general medical beds, respectively) multiplied by the duration of hospital stay. Taken that the cost of alternative uric acid lowering agent, febuxostat would be much higher than the cost of allopurinol, which was US$ 2.25 per 80 mg tablet per day versus US$ 0.234 per 200 mg tablet per day, we compared the annual cost of prescription of febuxostat to all patients without screening to that of the pre-treatment genotyping approach to evaluate the cost-effectiveness.

Results

Patient characteristics

Of the period 2006–2010, we screened 3605 patients who received allopurinol at the medical renal out-patient clinics in two tertiary hospitals (Queen Mary Hospital and Tung Wah Hospital) and included 1027 Chinese patients with CKD who were newly started on allopurinol as historic controls (Control group) (Table 1). We prospectively recruited 201 patients for HLA screening during the period of January 2011 to December 2015. After excluding the 9 subjects who were lost to follow-up or had withdrawn consent, 192 patients were included for data analysis (HLA screening group) (Fig. 1). A total of 1219 patients with CKD were included for analysis. In the HLA screening group, 28 patients (14.6%) were tested HLA-B*58:01 positive (Table 2) and were advised to avoid allopurinol. In the remaining 164 patients who were tested HLA-B*58:01-negative, 156 patients (95.1%) had received allopurinol. Eight patients did not take allopurinol as symptom was relieved by non-steroid anti-inflammatory drug (NSAID) or colchicine and continued on diet control alone.

Table 1 Clinical characteristics of the HLA screening and historic control groups

Mean ± SD (range)	Subjects ($n = 192$)	Control[a] ($N = 1027$)	p value
Age, yrs	64.3 ± 15.8 (23–96)	64.6 ± 15.6 (23–98)	0.59
Male (%)	118 (60.9%)	717 (69.8%)	0.55
Ethnicity (Chinese)	192 (100%)	1027(100%)	-
Baseline renal function			
Serum creatinine (mmol/L)	296.3 ± 242.7	288.9 ± 202.1	0.75
eGFR (mL/min/1.73 cm^2)	29.3 ± 19.8 (3–89)	30.4 ± 16.8 (3–89)	0.47
CKD (Stage 3 or above)	178 (92.7%)	619 (60.3%)	0.53
Serum urate (μmol/L)	573.3 ± 143.8	493.1 ± 166.7	0.13
Allopurinol use			
Duration (months)	24.1 ± 11.6	59.5 ± 10.4[b]	-
Dosage of allopurinol	113.3 ± 43.0 (50–300)	163.6 ± 87.3 (50–300)	-
Co-morbidity			
Hypertension	144 (75%)	593 (57.7%)	< 0.01*
Diabetes mellitus	108 (56.3%)	328 (31.9%)	0.09

CKD chronic kidney disease; *eGFR* estimated glomerular filtration rate ml/min/1.73m^2

CKD Stage 1: eGFR > 90; Stage 2: 60–89; Stage 3: 30–59; stage 4: 15–29; stage 5: < 15

[a]Control group defined as new recipients of allopurinol during 2006–2010

[b]Till date of analysis 12.2019

*Statistically significant

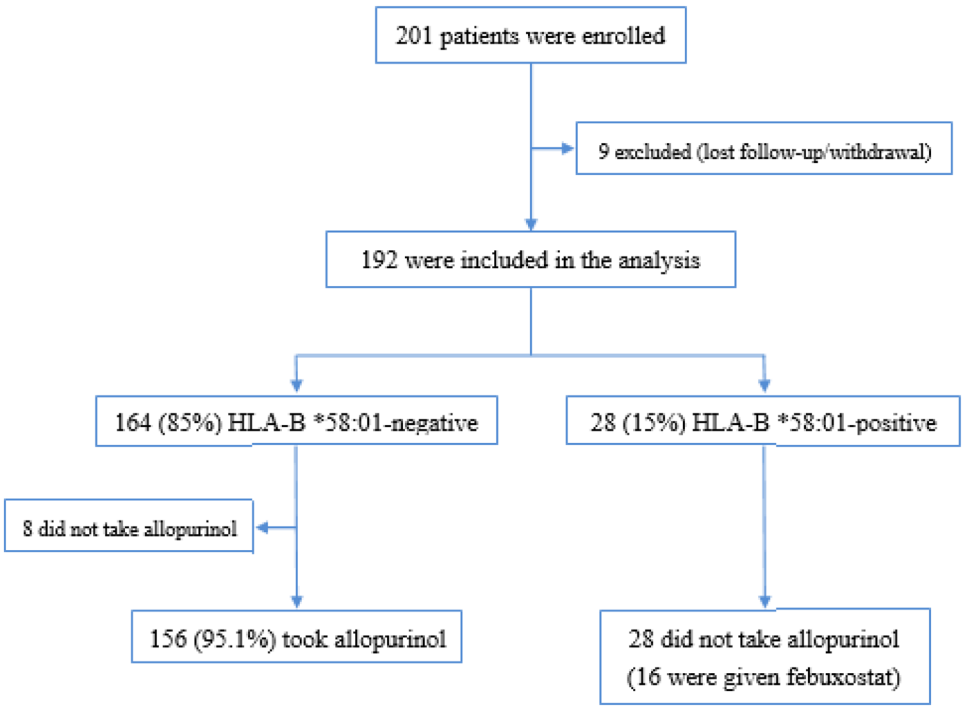

Fig. 1 Enrollment and outcomes. From 2011 to 2015, 201 subjects were recruited with blood sample collected. Twenty-eight out of 192 subjects (15%) were tested HLA-B*58:0 positive. They were advised not to take allopurinol. 156 subjects tested HLA-B*58:01-negative took allopurinol. No SCAR was reported

Development of SCARs and SJS/TEN

In the HLA screening group, one patient who concurrently received NSAID reported urticarial eruption after 6 days of allopurinol treatment and the urticaria subsided after discontinuation of both agents. Three HLA-B*58:01-negative patients experienced exacerbation of gout during the initial phase of allopurinol treatment but improved as the treatment continued. No patients developed SCARs or SJS/TEN in both HLA-B*58:01 positive and negative groups (Table 3).

For the Control group, 22 patients developed allopurinol-induced SCARs, including 16 (72.7%) DRESS/DHS and 6 (27.2%) SJS/TEN (Table 3). Nineteen (86.4%) patients had stage 3 or above CKD. Allopurinol was discontinued in

Table 2 Patient characteristics and adverse events in the HLA screening group ($n=192$)

	HLA-B*58:01 positive ($n=28$)	HLA-B*58:01-negative ($n=164$)
Age	65.4 ± 14.6 (41–94)	63.9 ± 15.9 (23–96)
Male	20 (71.4%)	99(60.3%)
eGFR (mL/min/1.73 m^2)	29.8 ± 20.2	29.3 ± 19.7
CKD stage 3 or above	28 (100%)	147 (89.6%)
Medication use		
Allopurinol	0	156 (95.1%)
Febuxostat	16 (57.1%)	–
Colchicine or NSAIDs	12 (42.9%)	46 (28.1%)
Adverse cutaneous reactions		
Onset of symptoms (days)	–	16.7 ± 11.8
Mild	0	1 (0.61%)[a]
Severe (SCARs)	0	0
Other	0	3[b] (1.82%)

[a]1 subject developed urticarial eruption and subsided after allopurinol discontinuation

[b]Worsening of joint swelling of foot/hand/digits during initial few weeks of allopurinol

Table 3 Characteristics of patients with allopurinol-induced SCARs in historical control group over 5-year period (2006–2010)

Mean ± SD	SCARs ($n=22$)
Age, years	63.8.5 ± 18.0
Male *n* (%)	11(50%)
Ethnicity (Chinese)	22 (100%)
SCARs	
DRESS	16 (72.7%)
SJS/TEN	6 (27.3%)
Baseline renal function	
Serum creatinine level (mmol/L)	196.7 ± 124.1
eGFR (mL/min/1.73 cm^2)	51.23 ± 34.32
CKD (Stage 3 or above) *n*, (%)	19 (86.4%)
Urate (μmol/L)	488.8 ± 159.7
Allopurinol use	
Duration (weeks)	9.57 ± 7.57
Dosage (mg/day)	193.75 ± 92.87
SJS/TEN, $n=6$	
Hospital stay (days)	18.5 ± 10.37
Use of IVIg, *n* (%)	3 (50%)
Use of systemic corticosteroid	3 (50%)
Ocular complication	3(50%)
ICU admission	4 (67%)
Duration (d)	10.5 ± 4.03
Mortality	1 (16.7%)
Hospital cost (USD), per person[a]	37,279 ± 15,826
Total cost (USD)	223,674

n (%) number (percentage); *d* days; *USD* US dollars

[a]Hospital cost: calculated by daily cost of hospital stay in ICU/HDU plus general wards multiply by duration of hospital stay divided by number of patients who developed SJS/TEN related to allopurinol

these 22 patients. For the 6 SJS/TEN patients, three patients underwent HLA-B*58:01 genotyping and all were positive (3/3, 100%), while the HLA-status of other three patients was not tested. Four DRESS/DHS patients underwent HLA-B*58:01 genotyping, of whom all were positive (4/4, 100%). The mean duration of hospital stay for DRESS/DHS cases was 5.5 ± 7.0 (range 3–22) days; SJS/TEN cases was 18.5 ± 10.3 (range 6–37) days; 66.7% (4 out of 6) required intensive care support for 10.5 ± 4.0 days (Table 3). Half of the patients (50%) required intravenous immunoglobulin therapy and 50% required systemic corticosteroid (prednisolone 1 mg/kg/day or equivalent). One patient died as a result of SJS/TEN. Three (50%) patients (2F:1M, age of 52–75 years, mean 60.3), had mild to moderate ocular complications of SJS/TEN (conjunctivitis, keratoconjunctivitis and corneal epithelial defect) and were managed conservatively during the acute stage with topical antibiotics (preservative free levofloxacin 0.5% eyedrops), topical steroids (prednisolone acetate 1% eye drops) and preservative free artificial tears, glass rod application on corneal adhesion. None of the patients required amniotic membrane transplantation during the acute stage. On long-term follow-up, one patient developed symblepharon of right lower eyelid with cornea scarring as a result of persistent ocular surface inflammation and eyelid margin keratinization, with subsequent visual impairment; and one patient developed right superior corneal pannus without symblepharon or significant limbal stem cell deficiency. There was no resulting visual impairment for the latter patient.

The HLA screening group showed a significantly lower incidence rate of allopurinol-induced SCARs compared with the Control group (0% vs 2.14%, $p=0.037$*) (Table 4). The relative risk (RR) of developing allopurinol-induced SCARs

Table 4 Incidence of allopurinol-induced SCARs in historical control (2006–2010) compared to HLA screening group

	Control ($N=1027$[a])	Study ($n=184$[b])	p value
Allopurinol-induced SCARs	22	0	–
Incidence of allopurinol-induced SCARs	2.14%	0%	0.037*

N number of new CKD patients receiving allopurinol in renal clinics of two tertiary hospitals in control; *SCARs* severe cutaneous adverse reactions

[a]Patients were excluded who started allopurinol use before 1st January 2006 or consumption less than 12 weeks

[b]CKD patients started on allopurinol ($n=156$) and patients avoided allopurinol due to HLA-B*58:01 carrier state ($n=28$) in HLA screening group

in the HLA screening group were 0.12 (95% CI 0.0075–2.23, $p=0.14$). For further sub-group analysis, in CKD stage 3 or above patients, the incidence of allopurinol-induced SCARs was even higher (3.07%, 19 out 619 patients with stage 3 or above CKD, compared to 0%, 0 out of 192 screening group subjects developed SCARs; $p=0.011$*, with post hoc power > 80%; RR = 0.08, 95% CI 0.005–1.41, $p=0.08$).

Cost-effectiveness of HLA screening

Using our historic controls as a cost-effectiveness analysis model, the cost of universal pre-treatment HLA screening in all controls was US$ 92,430 (i.e. US$ 90/test × 1027 patients). Based on our present data, the implementation of pre-treatment HLA screening would completely abrogate the occurrence of SCARs. Taken that a daily local hospital cost for Intensive care units and general wards was US$ 3128 and US$ 654, respectively, multiply the duration of hospital stays, the total cost of hospitalization of patients with SCARs was US$ 281,226; in particular, US$ 37,279 (in average) per SJS/TEN patient × 6 cases + US$ 3597 per DRESS/DHS patient × 16 cases, which was three-fold higher than performing HLA screening test. Thus, pre-treatment HLA screening can potentially reduce the health cost by 67.1% (US$ 92,430 with screening vs US$ 281,226 without screening).

Concerning the pharmaceutical cost, taken that the annual cost of febuxostat was US$ 821.25 per year (calculation: US$ 2.25 per 80 mg tablet febuxosat × 365 days), if we prescribed alternative uric acid lowering agents—febuxostat to patients without HLA screening, it would cost US$ 157,680 per year (calculation: US$ 821.25 × 192 patients), which would be significantly higher than that of the HLA screening/allopurinol approach, costing only US$ 54,282 [(US$ 90 per HLA test × 192 patients = US$ 17,280) + (US$ 0.234 per 200 mg daily dose of allopurinol × 365 days × 164 patients with negative HLA-B*58:01 status = US$ 14,007) + (US$ 2.25 per 80 mg daily dose of febuxostat × 365 days × 28 patients with positive HLA-B*58:01 status = US$ 22,995)]. Again, pre-treatment HLA screening approach can reduce the health cost by 65.5%.

Discussion

The incidence of SJS and TEN was estimated to be about 1–2 per million persons (PMP) per year and 0.4–1.2 PMP per year, respectively [20]. The mortality rate of SJS/TEN can be as high as 30–50% and 80% cases related to medications such antibiotics, anticonvulsants and uric acid lowering drugs [20, 21]. The pathogenetic mechanisms for drug-induced SCARs and SJS/TEN are highly complex and remain poorly understood. Drug-specific CD8 + lymphocytes have been detected in early blister fluid in SJS/TEN, while cytokines such as granzyme, perforin and natural killer cells directly causing damage to keratinocytes have also been implicated in the pathogenesis of drug-induced SCARs and SJS/TEN [22, 23]. Allopurinol is a xanthine oxidase inhibitor that is commonly used to treat hyperuricemia and gouty arthritis. It accounts for 5% of SCARs including SJS/TEN [24, 25]. It was suggested that HLA-B*58:01 carrier state was necessary but not sufficient for allopurinol-induced SCARs. Other co-factors such as renal insufficiency or viral infection have been implicated in the development of SCARs [4, 26, 27]. Studies have shown a relationship between allopurinol-induced SCARs and decreased creatinine clearance—patients with chronic kidney disease (CKD) had an increased risk of allopurinol-induced SCARs by five-fold [27, 28]. Allopurinol dosage adjustment have been suggested to reduce incidence of SCARs in renal insufficiency patients; however, studies failed to show the significant effect on reducing allopurinol hypersensitivity reactions [10, 29].

Our current data demonstrated that a HLA screening approach before the initiation of allopurinol can effectively prevent SCARs in CKD patients. Here we observed that the incidence rate of SCARs was significantly lower in HLA screening group compared with historic controls (0% vs 2.14%). Our results also suggested that a pre-treatment HLA screening approach reduced the risk of SCARs in CKD patients by 88% (RR = 0.12) although this did not reach statistical significance possibly due to the relatively small sample size and rarity of events. Notwithstanding, one should appreciate that no patient developed SCARs or SJS/TEN in the pre-treatment HLA screening group and this is extremely important because SJS/TEN is highly debilitating and potentially fatal. Moreover, SJS/TEN is not only associated with prolonged hospitalization (often in the intensive care unit (ICU)/burn units) and potential ocular sequalae and blindness, but also the use of costly therapies such as intravenous

immunoglobulin (IVIg). The results were not surprising as HLA-B*58:01 showed very strong association with the development of SCARs and SJS/TEN, especially in patients of Han Chinese and Asian descents [30–32], and in some European countries [33–35]. Aside from SJS/TEN, there has been a number of reports on a potential association between HLA-B*58:01 and SCARs, although different studies have shown considerable variations in the magnitude [29, 30, 36]. The risk of allopurinol-induced SCARs was substantially elevated in HLA-B*58:01 carriers, showing > 150-fold risk higher than allopurinol-tolerant controls with negative status [36, 37]. In a Taiwan cohort study on allopurinol-induced SCARs, HLA-B*58:01 was not only strongly associated with the occurrence of SCARs but its status also correlated with disease severity [28]. HLA-B*58:01 carriers had 5 times higher risk in developing SCARs than in maculopapular exanthema (OR 44 and 8.5, respectively). Moreover, the gene dosage effect of HLA-B*58:01 also influenced the development of allopurinol-induced SCARs. HLA-B*58:01-homozygous patients have 4.8 times higher risk than heterozygotic carrier, with OR of 72 and 15, respectively. Furthermore, patients with CKD are shown to be more susceptible to allopurinol-induced SCARs, posing 85-fold risk of allopurinol-induced SCARs in HLA-B*58:01carriers than those with normal renal function (OR 1269 vs 15, respectively) [28]. Based on these observations and our present data, it is reasonable to advocate HLA screening in patients who were to commence allopurinol, especially in high-risk subjects such as those with pre-existing CKD.

While it was intuitive that universal pre-treatment HLA screening can help prevent SCARs and SJS/TEN patients receiving allopurinol, the financial implications and cost-effectiveness remains valid concerns in the implementation of such program. In this study, we explored whether focusing on high-risk patients (i.e. patients with CKD) might enhance the cost-effectiveness of pre-treatment HLA testing. Indeed our results showed that targeted pre-treatment HLA screening is associated with much lower overall healthcare costs than not instigating HLA testing. While not performing HLA screening may save costs for genetic test and only a small number of patients will develop SCARs or SJS/TEN, one should be cognizant that patients who developed SJS/TEN would incur substantial healthcare burden as a result of prolonged stay in ICU/burn units and expensive salvage therapies for this condition. Patients with SCARs also required assessment/care by qualified dermatologists and additional medications. Our results were consistent with recent studies from Taiwan [38] and Korea [39, 40] which also showed the cost-effectiveness of HLA-B*58:01 screening in preventing allopurinol-induced SCARs in CKD patients. Furthermore, our calculations have not taken into account the long-term disability, disfigurement and mortality related to SJS/TEN. In this study, we also presented the drug costs if we were to commence febuxostat in all patients without HLA screening. Although this approach has the advantage to initiate immediately at the clinic setting, the annual drug costs are significantly higher than the HLA screening/allopurinol approach and thus have considerable impacts on drug budgets. While our data demonstrate that pre-treatment HLA-B*58:01 allele screening is cost-effective in Han Chinese CKD patients to prevent allopurinol-related SCARs, one should appreciate that these cost-effectiveness analysis data may not always be extrapolated to other populations/localities due to the differences in allele frequency of HLA-B*58:01, costs and availability of HLA testing and other medical facilities. As substantial difference in the genetic make-up and mixing of different minor ethnicities exist between Northern and Southern Chinese as well as in other countries, further studies are required to validate our findings in other populations. To prevent SCARs, while clinicians should consider HLA-B*58:01 pre-screening in Han Chinese adults with CKD and that of Asian countries such as Korean or Thai descent before initiating allopurinol therapy, for populations such as Caucasians, with gene frequency of only 1%, this test is not likely to be cost-effective, and the net benefit is not known [41, 42].The relatively small sample size remains an important limitation of this study, which may jeopardize the power to detect the rare occurrence of SJS/TEN. However, there are considerable resource implications and difficulty in conducting large-scale prospective study to address this clinical question and comparison with historic controls as in our study appeared to be a feasible and reasonable study design. Other limitations of using historic controls include the difference in general medical care and treatment approaches that may affect overall patient outcomes and cost-effectiveness analysis.

Conclusion

Pre-treatment HLA-B*58:01 screening can prevent allopurinol-induced SCARs in Chinese CKD patients and is cost-effective.

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Declarations

Conflict of interest There is no competing conflict of interest from all authors.

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