



Immunopathogenesis and risk factors for allopurinol severe cutaneous adverse reactions

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Purpose of review

The article reviews the immunopathogenesis and risk factors related to allopurinol-induced severe cutaneous adverse reactions (SCARs).

Recent findings

For years, allopurinol remains one of the leading cause for SCARs worldwide. The pathogenesis of allopurinol-induced SCARs have been discovered in recent years. HLA-B*58:01 has been found to be strongly associated with allopurinol-SCARs with functional interactions between allopurinol/its metabolite-oxypurinol and the T-cell receptor (TCR). However, the genetic strength of HLA-B*58:01 may vary among different ethnic populations. In addition to HLA-B*58:01, specific T cells with preferential TCR clonotypes, which have no cross-reactivity with new xanthine oxidase inhibitors structurally different from allopurinol, are found to play a crucial role for allopurinol-induced SCARs. Furthermore, other nongenetic factors such as renal impairment are also found to be an important factor resulting in allopurinol-induced SCARs of greater severity and poorer prognosis.

Summary

There are multiple risk factors for allopurinol-induced SCARs, including genetic and nongenetic factors. Activation of specific T cells with preferential TCR and its functional interaction of HLA-B*58:01 molecule and allopurinol/oxypurinol are involved in the immune mechanism of allopurinol-induced SCAR. Patients with allopurinol-induced SCARs with renal impairment have significantly higher risk of mortality. A structurally different new generation xanthine oxidase inhibitor can provide a safer alternative for patients intolerant to allopurinol.

Keywords

allopurinol, HLA-B*58:01, renal impairment, severe cutaneous adverse reactions, T-cell receptor

INTRODUCTION OF GOUT AND ALLOPURINOL

Allopurinol is the first-line urate lowering therapy (ULT) globally prescribed for gout and hyperuricemic patients since the 1960s [1]. There is increasing worldwide prevalence and incidence [2[¶],3] of gout and hyperuricemia especially among elderly populations. Important comorbidities and risk factors associated with gout include obesity, hypertension, chronic kidney disease (CKD) and cardiovascular disease (CVD) [3,4[¶]]. Some medications, like diuretics [5] and low-dose aspirin [6] contribute to elevated serum uric acid levels and increase the risk of incident gout.

Oxypurinol, the functional metabolite catalyzed from allopurinol, acts as a xanthine oxidase inhibitor to directly inhibit the oxidation of hypoxanthine and xanthine, resulting in the reduction of serum urate production. So far, allopurinol remains the ULT of choice as it is effective, cheap,

and easy to administer for patients with hyperuricemia [7]. However, it may induce adverse drug hypersensitivity reactions, ranging from mild maculopapular eruption to life-threatening severe cutaneous adverse reactions (SCARs), such as Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN) and drug reaction with

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KEY POINTS

- Allopurinol 'has a high risk' for inducing life-threatening SCARs, such as SJS/TEN and DRESS.
- HLA-B*58:01 and nongenetic factors (e.g. poor renal function) are associated with allopurinol-induced SCARs.
- HLA-B*5801 allele is strongly associated with allopurinol-induced SCARs; however, it is not 100% predictive and its strength of association may vary among different ethnic populations.
- A structurally different new generation xanthine oxidase inhibitor can have low potential to cause cross-hypersensitivity for allopurinol SCAR patients and provide a safer alternative for patients with allopurinol-induced SCARs.

eosinophilia and systemic symptoms (DRESS) (Fig. 1). Allopurinol is one of the leading causes for SCARs in Asian as well as Western countries [8,9].

Risk factors for allopurinol-induced severe cutaneous adverse reactions

Although the administration of allopurinol is usually tolerable for patients receiving ULT, a few patients may develop hypersensitivity reactions. About 1–5% of allopurinol users present with minor adverse reactions [10]. Allopurinol-induced SCARs has been observed in approximately 0.4% of new users, with a high mortality of between 9 and 32% [8,11,12]. Patients with allopurinol-induced SCARs may die from multiorgan failure or infection. Several studies have demonstrated increased allopurinol prescriptions [13–16] because of the increasing worldwide prevalence of gout [17^{••},18], with a rise in prevalence of allopurinol-induced

SCARs as a consequence. We recently reported a significant increase in the annual incidence of allopurinol hypersensitivity and allopurinol new users among patients with asymptomatic hyperuricemia [19^{••}]. This study was analyzed by comparing the data in 2005 and in 2011 from Taiwan's National Health Insurance Research Database, which belongs to the nationwide population database with more than 23 million insured enrollees. There were approximately 4.68/1000 new users with allopurinol hypersensitivity [19^{••}]. Moreover, the hospitalization rate of allopurinol new users related to hypersensitivity was also significantly increased (up to 2.02/1000 new user) with high mortality (0.39/1000 new user) [19^{••}].

Until now, there are several risk factors for allopurinol-induced SCARs which have been identified, including HLA-B*58:01 carrier, older age, female gender, high allopurinol initial dosage, and patients with poor renal function or CVD (Fig. 2).

Pharmacogenomics of allopurinol hypersensitivity

A previous systemic review analyzed a total of 901 patients with allopurinol hypersensitivity during the period 1950 to 2012. This showed that populations from Europe, Africa, Americas, and Oceania accounted for 14.1, 6.78, 5.25, and 1.02% of allopurinol hypersensitivity, respectively. Asian ancestry comprised the largest portion of 73% [12]. The result could be interpreted in relation to the genetic factors and allopurinol hypersensitivity. In 2005, we first identified that HLA-B*58:01 allele is strongly associated with allopurinol-induced SCARs in the Han Chinese population, which enrolled a group of 51 patients with allopurinol-induced SCARs, 228 allopurinol tolerant controls and

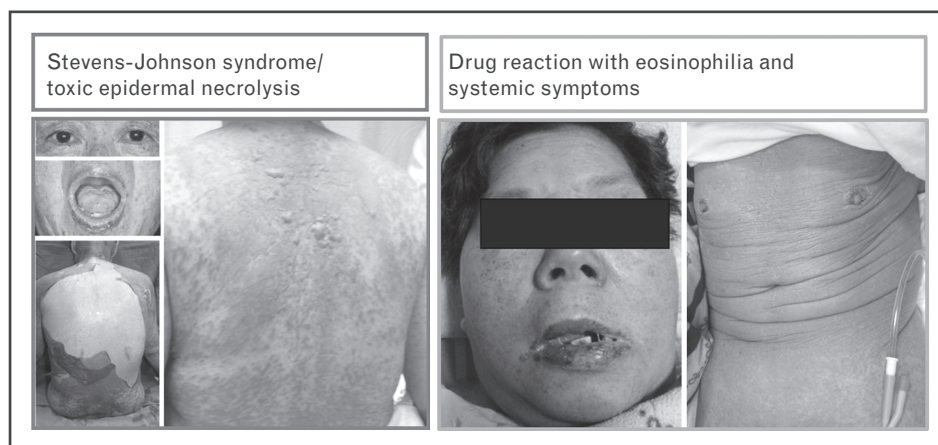


FIGURE 1. Clinical presentations of allopurinol-induced severe cutaneous adverse reactions. Reproduced with patient consent. SCARs, severe cutaneous adverse reactions.

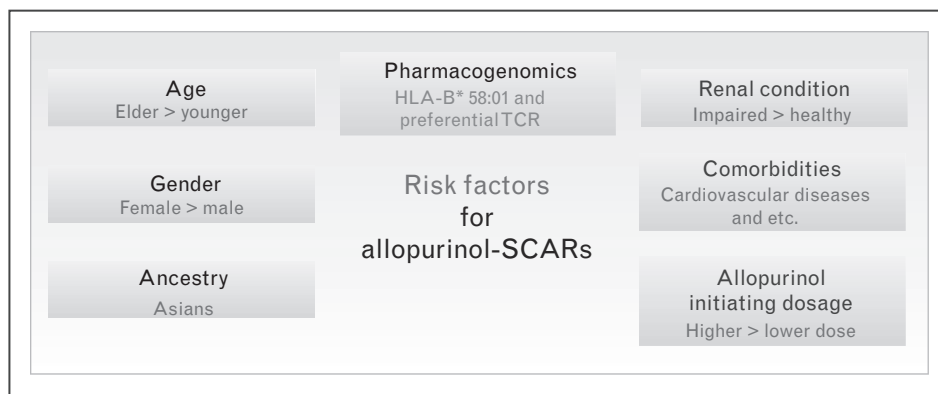


FIGURE 2. Risk factors for allopurinol-induced severe cutaneous adverse reactions. SCARs, severe cutaneous adverse reactions.

93 healthy individuals [20^{***}]. The association was also reported among the Japanese [21], Europeans [22], Thais [23], and Koreans [24]. HLA-B*58:01 allele associated with allopurinol-induced SJS/TEN as well as allopurinol-induced DRESS has been found in different populations, although the genetic strength may vary among different ethnic groups.

The prevalence of gout is one of the factors responsible for the risk of allopurinol-induced SCARs. Several studies have shown a lower prevalence of 0.09% gout in China [25], in contrast to higher rates of 3.24 and 4% in Caucasian populations from New Zealand [26] and the United States [27], respectively. As we have found the strong association between HLA-B*58:01 and allopurinol-induced SCARs in Han Chinese, the allele frequency becomes important in these studies. HLA-B*58:01 allele frequency had been reported as more than 10% in the Southeast Asian population and 1~2% in Japan and Western European populations (Fig. 3; data from allele

frequency net database; <http://www.allelefrequency.net/>) [28]. This suggests that the genetic strength of HLA-B*58:01 actually plays a crucial role for the development of allopurinol-induced SCARs. However, our updated follow-up study ($n = 146$) found that the HLA-B*58:01 allele is not 100% predictive and is not present in some patients with allopurinol-induced SCARs, even in the most relevant Asian populations. Our updated data show at least 16% of Chinese patients of allopurinol hypersensitivity who do not carry the HLA-B*58:01 allele (Ng CY *et al.*, J Invest Dermatol. 2016, unpublished). The low positive predictive value and variable negative predictive value of HLA-B*58:01 for allopurinol-induced SCARs suggest that other factors may contribute to the pathogenesis of allopurinol-induced SCARs.

Allopurinol dosage, renal function and metabolism

Over the past decades, allopurinol metabolism has been considered as one of the key factors in the development of allopurinol-induced SCARs. Firstly, Hande *et al.* [29] determined that the starting dose of allopurinol should be reduced in patients with poor creatinine clearance to reduce the incidence of allopurinol toxicity. Stamp, L.K. and coworkers found the relationship between allopurinol dosage and renal function by evaluating the estimated glomerular filtration rate (eGFR) in 54 cases with allopurinol-induced SCARs and 157 allopurinol-tolerant controls. They found that when the initial allopurinol dosage was more than 4.05 mg/unit of eGFR, an increase risk of allopurinol-induced SCARs was obviously observed [odd ratio (OR) = 23.2; $P < 0.01$]. Their result also revealed that an allopurinol initial dosage of less than 1.5 mg/unit of eGFR may be associated with a reduced risk of allopurinol hypersensitivity [30].

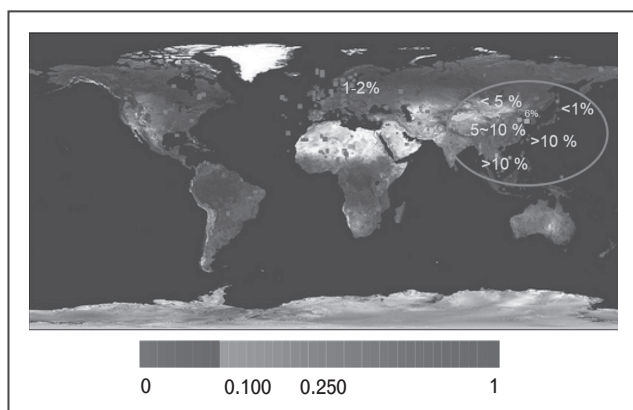


FIGURE 3. The allele frequency of HLA-B*58:01 in worldwide population. Data were from allele frequency net database.

The kidney is the major organ for the excretion of oxypurinol. Therefore, the clearance of oxypurinol and sustained plasma levels of oxypurinol are determined by renal function. We recently reported the pathomechanism between renal insufficiency and allopurinol-induced SCARs [31[■]]. In this study, we analyzed 48 patients with allopurinol-induced SCARs and 138 allopurinol-tolerant patients. We found that the baseline eGFR of allopurinol-induced SCARs patients (34.0 ± 29.0 ml/min/ 1.73 m²) was significantly lower than the tolerant controls (67.5 ± 32.4 ml/min/ 1.73 m²) ($P < 0.001$), and patients with severe renal impairment (eGFR < 30 ml/min/ 1.73 m²) were associated with 60% of allopurinol-induced SCARs cases and only 15.9% of the tolerant controls. Patients with renal insufficiency showed an 8-fold risk ($P < 0.001$) for allopurinol-induced SCARs. In addition, we found that the allopurinol-induced SCARs patients with severe renal impairment had higher levels of plasma oxypurinol than those with normal renal function. Comparing with the tolerant controls, the allopurinol-induced SCARs patients with severe renal impairment maintained higher levels of plasma oxypurinol, and delayed oxypurinol clearance for as long as 2 weeks after discontinuation of allopurinol. This indicates that impaired renal function indeed increases the risk for allopurinol-induced SCARs. In addition, we also found that renal impairment accompanied by delayed clearance of oxypurinol was significantly associated with poor prognosis of allopurinol-induced SCARs [31[■]].

Age and gender

Allopurinol-induced SCARs has been found to be more frequent among elderly patients. Our recent nationwide population-based study [19[■]] has reported that its incidence predominantly increased in new allopurinol users aged 60 years or above. The incidence of allopurinol-induced hypersensitivity was higher among older patients, with an OR of 2.27 ($P < 0.001$). Mortality was also showing higher (OR, 12.37; $P < 0.001$) in older patients, particularly those 80 years or older [19[■]]. In addition, this study [19[■]] also showed that women had a higher risk for allopurinol-induced hypersensitivity (OR, 1.45; $P < .001$) and related mortality (OR, 1.63; $P < .001$) than men. The reason for higher risk of allopurinol hypersensitivity among elderly female patients is still unknown. The elderly patients with allopurinol-induced SCARs may have lower metabolism for oxypurinol than younger patients. Furthermore, previous studies have shown that the risk of CKD was significantly higher in female patients with hyperuricemia than in male patients. The estrogen

effect on renal clearance of uric acid has been postulated [32,33], and that may partially explain the higher risk in female patients.

Comorbidities

Previous studies [34–39] suggest that patients with asymptomatic hyperuricemia and several comorbidities, including CKD, CVD, and metabolic diseases, may have higher plasma uric acid levels and contribute to the prognosis of hyperuricemia. However, the risks of these comorbidities for allopurinol use in asymptomatic hyperuricemia are not fully understood. In our recent study [19[■]], allopurinol prescription to patients with asymptomatic hyperuricemia showed a statistically increased risk of allopurinol hypersensitivity in patients with CKD or CVD. Results of multivariable logistic regression showed that the comorbid CKD and CVD increased the risk (OR, 1.61; $P < .001$ for CKD and OR, 1.52; $P < .001$ for CVD) and mortality (OR, 5.59; $P < .001$ for CKD and OR, 3.57; $P < .001$ for CVD) of allopurinol-induced hypersensitivity [19[■]]. Physicians need to be cautious when prescribing allopurinol to patients with the comorbid CKD and CVD.

MECHANISMS AND IMMUNOPATHOGENESIS OF ALLOPURINOL-INDUCED SEVERE CUTANEOUS ADVERSE REACTIONS

It has been known that the drug-specific CD4⁺ and CD8⁺ T cells are responsible for pathogenesis of SCARs. In general, the HLA molecules present drug antigen to the T-cell receptor (TCR) [40] and the complex HLA-drug-TCR initiates the cascade of immune responses (Fig. 4). A recent study [41[■]] showed a pharmacological interaction (p-i) concept was considered as the main interaction model between the HLA-B*58:01 molecule and allopurinol or its metabolite oxypurinol. Lin *et al.* [41[■]] showed a direct interaction of the HLA-B*58:01 molecule with allopurinol/oxypurinol and demonstrated that the Arg97 of HLA-B*58:01 serves as the most probable binding site for oxypurinol via the hydrogen bond forming. This finding revealed the functional role of the HLA-B*58:01 protein with interaction and activation of oxypurinol-specific T cells.

For immunopathogenesis of SCARs, we previously identified that granulysin, a 15-kDa secretory form of cytotoxic molecule released by cytotoxic T lymphocytes, natural killer and NKT cells, was expressed in the blister fluids of skin lesions and was responsible for the disseminated keratinocyte death of SJS/TEN [42]. Furthermore, knockdown of granulysin mRNA expression by

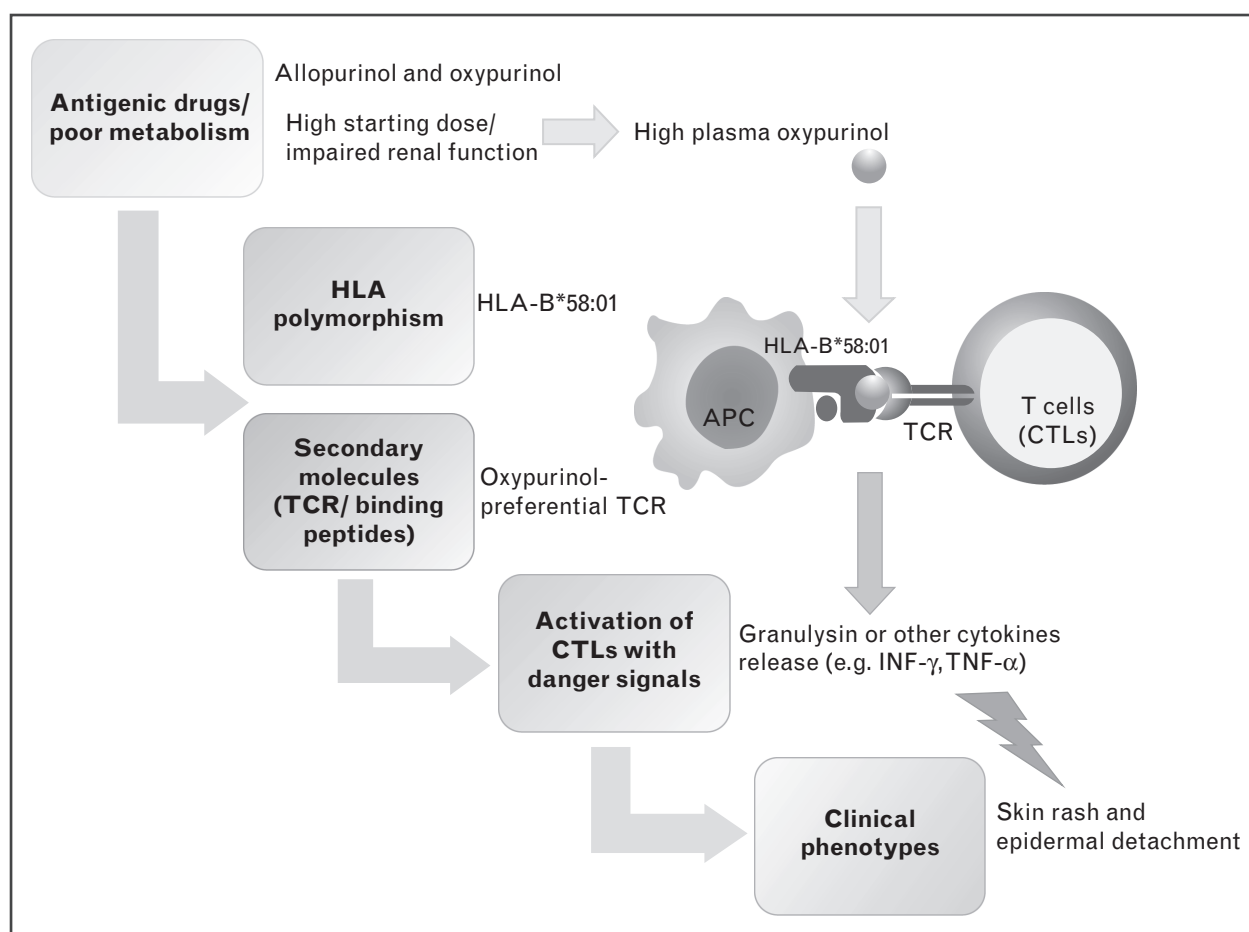


FIGURE 4. Molecular mechanism of allopurinol-induced severe cutaneous adverse reactions. Allopurinol-induced SCARs are initiated by the binding of the antigenic drug, allopurinol or its major metabolite oxypurinol, to the HLA-B*58:01 of the antigen presenting cells, which then triggers a cascade of cytotoxic T lymphocytes (CTLs)-associated immune responses, and results in skin rash or epidermal detachment. APC, antigen presenting cells; SCARs, severe cutaneous adverse reactions.

granulysin siRNA-based agents can significantly inhibit allopurinol-specific T-cell-mediated cytotoxicity [43]. Granulysin is a key mediator for allopurinol-induced SCARs. In addition to granulysin, other cytokines, such as TNF- α and IFN- γ , have also been shown to be strongly expressed in SCARs patients and are involved in pathogenesis of SCARs [44–46].

We recently reported an in-vitro T-cell activation assay to measure granulysin release by stimulating allopurinol-induced SCARs patients' peripheral blood mononuclear cells upon allopurinol, oxypurinol, or febuxostat [47^{***}]. The results showed that secreted granulysin was significantly increased by oxypurinol in a dose and time-dependent manner from oxypurinol-induced T-cell responses, but not by allopurinol and febuxostat which is a structurally different new generation xanthine oxidase inhibitor. The drug-specific T cells from patients with allopurinol-SCARs showed no

cross-reactivity with febuxostat and this observation was also supported by clinical follow-up of enrolled patients with allopurinol-SCARs who tolerated febuxostat. We further identified the preferential TCR-V- β usage and specific Complementarity Determining Region 3 (CDR3) of TCR in the blister cells from patients with allopurinol-SCARs [47^{***}]. The study suggests that the oxypurinol-specific T cells possessing preferential TCR and secreting granulysin were also involved in the pathogenesis of allopurinol-induced SCARs.

PREVENTION OF ALLOPURINOL-INDUCED SEVERE CUTANEOUS ADVERSE REACTIONS

Since the association between HLA-B*58:01 and allopurinol-induced SCARs was discovered in 2005, the HLA genetic testing for new allopurinol users has become important, especially in Southeast Asia. In

2009, the Food and Drug Administration in Taiwan issued a suggestion for avoidance of prescription of allopurinol in patients carrying HLA-B*58:01. Furthermore, the American College of Rheumatology guideline recommends HLA-B*58:01 genetic testing for first-time allopurinol users in Asian populations [48]. Recently, a national cohort study evaluated the use of prospective screening for the HLA-B*58:01 in Taiwan. This study [49] has reported that SCARs did not develop in any patients taking allopurinol who were non-HLA-B*58:01 carriers ($n = 2339$). With the prior-to-prescription screening of HLA-B*58:01, the incidence rate of allopurinol-induced SCARs was reduced in Taiwan. The strategies employed by the government for the prevention of allopurinol-induced SCARs include HLA-B*58:01 gene detection, but this may not be cost-effective, especially in non-Asians or Japanese.

Slow titration of allopurinol has been recommended to reduce allopurinol hypersensitivity, especially for patients with impaired renal function. Starting lower allopurinol dosage for new users may not prevent allopurinol hypersensitivity, but it may reduce severity at the onset of hypersensitivity reactions for patients who are susceptible to allopurinol. However, a prolonged exposure of lower initial dosage without early discontinuation of allopurinol after onset of hypersensitivity may also increase the severity of allopurinol hypersensitivity and result in fatal adverse reactions. In clinical practice, slow titration with close monitoring for early symptoms and signs of hypersensitivity reactions for allopurinol new users is needed to reduce fatal outcomes of allopurinol-SCARs.

Febuxostat is a nonpurine-based selective xanthine oxidase inhibitor structurally different from allopurinol, and is relatively safer than allopurinol [50]. Patients with allopurinol-SCARs showed no cross-reactivity with febuxostat [47²²,51]. The Scottish Medicines Consortium has approved febuxostat as a second-line medication where allopurinol is ineffective or contraindicated [52]. In Taiwan, the new xanthine oxidase inhibitor febuxostat has been changed to first-line use since 2014 in gout and hyperuricemia patients with poor renal function (eGFR <45). The drug is also reimbursable from National Institutes of Health. So far, no patient with febuxostat-induced SJS/TEN has been confirmed and reported in the literature. Two case reports showed that febuxostat could induce hypersensitivity and DRESS [53,54], and one study [53] revealed that febuxostat-induced adverse reactions were generally milder than allopurinol hypersensitivity reactions. Further pharmacogenetic and pharmacoeconomic studies comparing febuxostat and allopurinol are needed.

CONCLUSION

Although allopurinol is notorious for life-threatening SCARs, it has been used for the treatment of gout and hyperuricemia since 1966. For over a decade, with rapidly advanced biotechnology, scientists have provided more information about allopurinol-induced SCARs in the fields of pharmacogenetics, immunology, and pharmacology. For prevention of allopurinol-SCARs, multiple strategies should be carried out, including prospective HLA-B*58:01 screening, initial allopurinol dose adjustment with closer clinical monitoring, avoidance in patients with poor renal function, and use of new generation xanthine oxidase inhibitor for high risk patients.

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Conflicts of interest

There are no conflicts of interest.

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