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DIA

ORIGINAL RESEARCH

Allopurinol-Induced Severe Cutaneous Adverse Drug Reactions: An Analysis of Spontaneous Reports in Malaysia (2000–2018)

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Abstract

Introduction Allopurinol-induced severe cutaneous adverse drug reactions (SCARs) are potentially debilitating and life-threatening reactions, which can cause a financial burden to the healthcare system.

Objectives We aimed to identify risk factors for allopurinol-induced SCARs and to assess their impact on fatality.

Methods Adverse drug reaction (ADR) reports with allopurinol as suspected drug were extracted from the Malaysian pharmacovigilance database from year 2000 to 2018. Multiple logistic regression analysis was used to identify significant predictors of allopurinol-induced SCARs. We further analysed the association between covariates and SCARs-related fatality in a separate model. Level of significance was set at p value < 0.05.

Results Out of 1747 allopurinol ADR reports, 612 involved SCARs (35%). The strongest predictors significantly associated with SCARs were underlying renal disease (odds ratio [OR] 2.02; 95% confidence interval [CI] 1.36, 3.00; $p = 0.001$), allopurinol-prescribed dose of 300 mg/day or higher (OR 1.72; 95% CI 1.38, 2.15; $p < 0.001$), females (OR 1.54; 95% CI 1.24, 1.93; $p < 0.001$), age 65 years and above (OR 1.31; 95% CI 1.04, 1.64; $p = 0.020$), and allopurinol-prescribed indication. SCARs cases were higher in patients who received allopurinol for unspecified hyperuricaemia (OR 1.87; 95% CI 1.29, 2.70; $p = 0.001$) and off-label indications (OR 3.45; 95% CI 2.20, 5.42; $p < 0.001$) compared to registered indications. Fatality was associated with older age and a diagnosis of Stevens–Johnson syndrome/toxic epidermal necrolysis (SJS/TEN) overlap or TEN.

Conclusions Malaysian pharmacovigilance data show that predictors of allopurinol-induced SCARs were elderly females, patients with underlying renal disease and high allopurinol doses. These patients need close monitoring and must be educated to stop allopurinol at the first signs of rash.

Keywords Allopurinol · Severe cutaneous adverse drug reaction · Pharmacovigilance · Stevens–Johnson syndrome · Fatality

Introduction

Allopurinol is a medication to treat gout and a mainstay therapy for over 40 years worldwide. This is due to its benefits in treating urate overproduction and undersecretion with a once daily dosing [1, 2]. However, patients prescribed allopurinol face a known risk of developing severe cutaneous adverse drug reactions (SCARs) widely discussed in clinical practice guidelines [3, 4].

Allopurinol-induced SCARs include Stevens–Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), drug reaction with eosinophilia and systemic symptoms (DRESS), also known as drug-induced hypersensitivity syndrome (DIHS) and acute generalised exanthematous pustulosis (AGEP) [5]. Although rare, with an estimated incidence rate of 0.4% [6], SCARs can result in multiorgan injuries, prolonged hospitalisation, and death [7]. The mortality rates range from 5 to 10% for SJS and DRESS, and up to 30 to 40% for TEN [8]. Furthermore, the management of patient with SCARs poses an economic burden

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to the patients and the healthcare system [8, 9]. A study by Yang et al. [9] found that the total healthcare cost for the treatment of 73 SCAR patients in a Korean hospital was 752, 067 US dollars (USD), mostly from inpatient treatment. This cost increased significantly with duration of hospitalisation and death [9].

Pharmacogenomic studies have shown that genetic factors can predispose patients to SCARs and genetic markers enable screening of subjects. The human leukocyte antigen (HLA) genotypes associated with SCARs include *HLA-B*58:01* for allopurinol (Asians), *HLA-B*15:02* (Han Chinese) and *HLA-A*31:01* (Europeans and Koreans) for carbamazepine, *HLA-B*57:01* for abacavir (Caucasians), *HLA-B*59:01* for methazolamide (Koreans and Japanese), and *HLA-B*13:01* for dapsone (Asians) [10]. The variant allele, *HLA-B*58:01*, is strongly associated with allopurinol-induced SCARs. The frequency of the *HLA-B*58:01* allele varies significantly by population and most commonly found in Asian subpopulations, of Korean, Han Chinese, or Thai descent [2, 9].

In Malaysia, local clinical practice guidelines are available for the treatment of allopurinol [3] but genetic testing for *HLA-B*58:01* is not a prerequisite for treatment. Among all Adverse Drug Reaction (ADR) reports submitted to the World Health Organisation (WHO) global database, Malaysia was among the top ten countries to report ADRs related to allopurinol [11]. To date, no studies have been conducted to identify non-genetic factors or a specific group of patients who are more susceptible to allopurinol-induced SCARs in Malaysia. We therefore aimed to identify risk factors for allopurinol-induced SCARs from spontaneously reported ADRs to the national pharmacovigilance database and to assess their impact on fatality. Findings from this study will be useful for healthcare professionals to exercise caution when treating with allopurinol.

Materials and Methods

Study Design

This is a retrospective cross-sectional study of ADR reports from the national pharmacovigilance database in Malaysia. Established since year 2000, the database is located within the National Pharmaceutical Regulatory Agency (NPRA), Ministry of Health (MOH), Malaysia. All voluntary ADR reports received throughout the country from public or private healthcare facilities and pharmaceutical companies are collected and assessed here by the Malaysian Adverse Drug Reactions Advisory Committee (MADRAC) before they are submitted to the World Health Organisation (WHO) global database.

Data Extraction

ADR reports with allopurinol as the suspected drug from January 2000 to December 2018 were extracted. Reports that were assigned with causality "certain", "probable", or "possible" by using the World Health Organisation-Uppsala Monitoring Centre (WHO-UMC) causality assessment system were included for analysis [12]. The reports were screened to exclude possible duplication and to ensure that no other drug was suspected to cause the ADR. All relevant information were recorded as reported.

This study received ethical approval and permission to access the database from the MOH Medical Research and Ethics Committee [Ref: KKM/NIHSEC/P19-2132 (5)]. As the data are extracted from a database of spontaneously reported ADRs, it only contains an identifiable ADR report number, and patient information is anonymised. Thus, informed consent was not required. We obtained approval to conduct this study from the National Institute of Health [NMRR-19-2394-50036 (IIR)].

Selection of Allopurinol-Induced SCAR reports

To obtain SCAR-related ADR reports from the database, the allopurinol reports were screened according to Medical Dictionary for Regulatory Activities (MedDRA) System Organ Class (SOC) 'Skin and subcutaneous tissue disorders'. We used the RegiSCAR criteria for SCARS which included Stevens–Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), drug reaction with eosinophilia and systemic symptoms (DRESS), and acute generalised exanthematous pustulosis (AGEP) [5].

Study Variables

Covariates in this study were patient's age, gender, race, allopurinol-prescribed indication, allopurinol-prescribed dose (milligrams), types of SCARs, time-to-onset of reaction (days), outcome, and underlying renal disease (i.e. chronic kidney disease, renal impairment, end-stage renal disease, and acute on chronic kidney disease). For age, patients were categorised into two groups: less than 65 years old and 65 years old and above [13]. We classified allopurinol-prescribed doses according to < 300 mg/day and ≥ 300 mg/day to understand mild and moderate-to-severe conditions requiring treatment [2, 3].

Allopurinol-prescribed indications were further classified as registered, off-label, unspecified, or unknown. In Malaysia, allopurinol is registered for reducing urate/uric acid formation in conditions where urate/uric acid deposition has already occurred (e.g. gouty arthritis, skin tophi,

nephrolithiasis) or is a predictable clinical risk (e.g. treatment of malignancy potentially leading to acute uric acid nephropathy), the management of 2,8-dihydroxyadenine (2,8-DHA) renal stones related to deficient activity of adenine phosphoribosyltransferase and for the management of recurrent mixed calcium oxalate renal stones in the presence of hyperuricosuria, when fluid, dietary, and similar measures have failed [14].

Off-label indication for allopurinol in this study referred to ADRs reported as asymptomatic hyperuricaemia. Asymptomatic hyperuricaemia is a condition where serum urate level is abnormally high (male > 0.42 mmol/L or 7.0 mg/dL and > 0.36 mmol/L or 6.0 mg/dL in female) but no signs or symptoms of urate deposition have occurred [3]. Unspecified hyperuricaemia was chosen when serum urate level was stated to be above normal reference range with no additional information. All outcomes provided in the ADR reports were perceived as final during the time of reporting.

Statistical Analysis

Data analyses were conducted using IBM SPSS version 21 (SPSS Inc., Chicago IL, USA). Categorical data were presented in numbers or percentages, while numerical data were depicted in mean and standard deviation (SD) or median and interquartile range (IQR) where available.

To assess the association between the covariates and the occurrence of SCARs, univariable logistic regression was performed to provide a preliminary idea on variables to be included in subsequent multivariable logistic regression. Variables found not significant in univariable analysis but clinically relevant based on prior studies were forced into the model. The best fit model was selected by means of Hosmer–Lemeshow test, classification table, and area under the receiver operating characteristic (ROC) curve. Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated. Further, a separate logistic regression model was applied to determine the association between the covariates and fatality among all SCARs cases. All tests were two-sided, and level of significance was set at p value less than 0.05.

Results

ADR Reporting Trend

From year 2000 to 2018, a total of 144,507 ADR reports have been received. Out of this total, 1747 allopurinol reports were eligible to be included in the analysis (Fig. 1). Majority of these reports (92.5%) were classified as the SOC 'Skin and subcutaneous tissue disorders'. SCARs comprised 35% of these cutaneous-related reports. The second most reported SOC was 'General disorders and administration site conditions' such as fever and face oedema, followed by SOC 'Gastrointestinal disorders' such as lip swelling and mouth ulceration.

Characteristics of Allopurinol ADR Reports

For all allopurinol reports, more than half of the patients were male (55.7%) and 38.6% were more than 65 years of age. Malays constituted 51.7% of all patients, followed by Chinese (31.9%), Indian (2.3%), and other races (8.7%). Allopurinol was mainly prescribed for its registered indications (81.2%). However, 8.6% of patients received allopurinol for unspecified hyperuricaemia and 6% for off-label indication. There were 7.3% of patients reported to have underlying renal disease.

However, among allopurinol-induced SCARs cases, there were more females compared to males. In terms of indications, more patients were prescribed with allopurinol for off-label indication in SCARs cases compared to non-SCARs cases (10.6% vs 3.5%). The allopurinol-prescribed doses were also higher in SCARs cases (median: 300 mg/day; Interquartile range [IQR]: 150 mg) than non-SCARs cases (median: 150 mg/day; IQR: 150 mg). The number of patients who received more than 300 mg/day among the SCARs cases was higher than non-SCARs cases (48.5% vs 40.5%).

With regard to outcome, 47.5% of all patients were reported to have recovered, 28.2% had not recovered at the time of reporting, 10.9% were recovering, and 0.7% recovered with sequelae from the reaction. Fatality was reported in 87 (5.0%) of all allopurinol cases. Fatality was higher among those who experienced SCARs compared to non-SCAR patients (9.5% vs 2.6%). Table 1 shows the characteristics of patients who reported an ADR with allopurinol from year 2000 to 2018.

Types of Allopurinol-Induced SCARs

The most reported type of allopurinol-induced SCARs was SJS (57.5%) with the median time-to-onset of 19 days (IQR: 20), followed by DRESS (25.7%) with the median time-to-onset of 28 days (IQR: 9.8), and TEN (10.5%) occurring within 15 days (IQR: 23). A small number of SJS/TEN (4.7%) and AGEP (1.0%) were reported. There were four cases reporting both SJS and DRESS in a single report. Table 2 shows the types of SCARs reported and time-to-onset.

Risk Factors for Allopurinol-Induced SCARs

Patient's age, gender, allopurinol-prescribed indication, allopurinol-prescribed dose, and underlying renal disease were significantly associated with the occurrence of SCARs

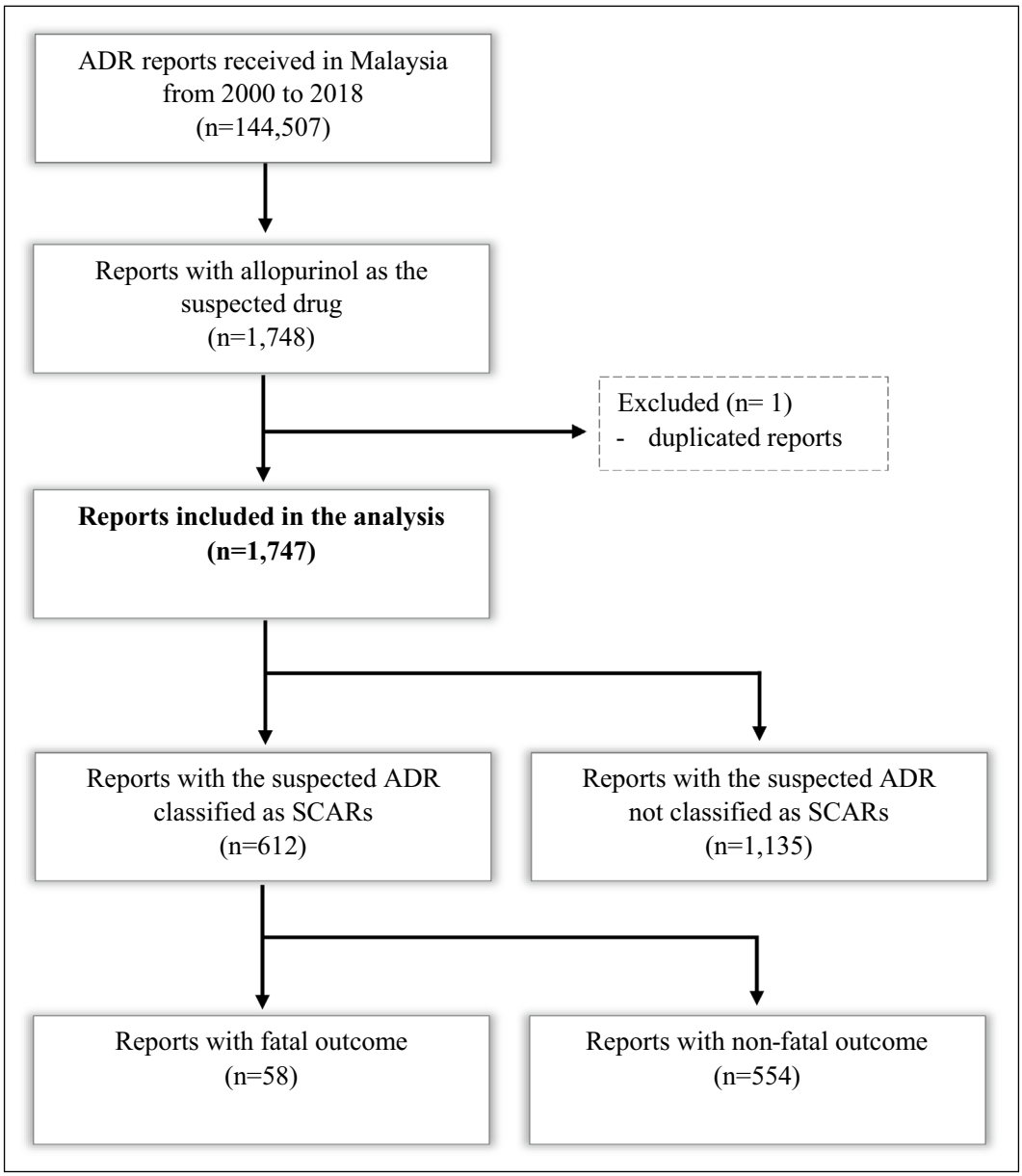

Figure 1 Flowchart of Allopurinol-Induced Severe Cutaneous Adverse Drug Reactions (SCARS) Selected for Analysis from Adverse Drug Reaction (ADR) Reports Received in Malaysia.

among all allopurinol reports. Patients aged 65 years and above were 1.31 times more likely to have SCARs (95% confidence interval [CI] 1.04, 1.64; $p = 0.020$) compared to their counterparts. Females were 1.54 times more likely to have SCARs (95% CI 1.24, 1.93; $p < 0.001$) compared to males.

Allopurinol-prescribed indications classified as unspecified hyperuricaemia were 1.87 times more likely to have SCARs reported (95% CI 1.29, 2.70; $p = 0.001$) as compared to allopurinol reports for registered indication. Reports classified as off-label indication were also 3.45 times more likely to have SCARs reported (95% CI 2.20, 5.42; $p < 0.001$). This shows that patients prescribed allopurinol for indications other than registered indications have a higher risk of SCARs.

In terms of dosing, allopurinol-prescribed dose of 300 mg or more daily was 1.72 times more likely to be associated with SCARs (95% CI 1.38, 2.15; $p < 0.001$). Cases reported with underlying renal disease were two times more likely to have SCARs (95% CI 1.36, 3.00; $p = 0.001$) compared to those who did not. Table 3 shows the risk factors for SCARs among all allopurinol reports from year 2000 to 2018.

Table 1 Patient Characteristics of Adverse Drug Reaction (ADR) Reports with Allopurinol as Suspected Drug from Year 2000 to 2018.

Patient demographics	SCARs[a] cases, *n* (%) (*n* = 612)	Non-SCARs[a] cases, *n* (%) (*n* = 1135)	Total cases, *n* (%) (*n* = 1747)
Age (years)			
< 65	356 (58.2)	694 (61.1)	1050 (60.1)
≥ 65	251 (41.0)	424 (37.4)	675 (38.6)
Unknown	5 (0.8)	17 (1.5)	22 (1.3)
Gender			
Male	294 (48.0)	679 (59.8)	973 (55.7)
Female	309 (50.5)	440 (38.8)	749 (42.9)
Unknown	9 (1.5)	16 (1.4)	25 (1.4)
Race			
Malay	320 (52.3)	584 (51.5)	904 (51.7)
Chinese	220 (35.9)	337 (29.7)	557 (31.9)
Indian	14 (2.3)	26 (2.3)	40 (2.3)
Others	41 (6.7)	111 (9.8)	152 (8.7)
Unknown	17 (2.8)	77 (6.8)	94 (5.4)
Indication			
Registered indication	452 (73.9)	967 (85.2)	1419 (81.2)
Unspecified hyperuricaemia	71 (11.6)	79 (7.0)	150 (8.6)
Off-label indication	65 (10.6)	40 (3.5)	105 (6.0)
Unknown	24 (3.9)	49 (4.3)	73 (4.2)
Allopurinol dose (mg)			
< 300 per day	245 (40.0)	596 (52.5)	841 (48.1)
≥ 300 per day	297 (48.5)	460 (40.5)	757 (43.3)
Unknown	70 (11.4)	79 (7.0)	149 (8.5)
Outcome			
Recovered	225 (36.8)	605 (53.3)	830 (47.5)
Recovering	73 (11.9)	118 (10.4)	191 (10.9)
Recovered with sequelae	8 (1.3)	5 (0.4)	13 (0.7)
Not yet recovered	207 (33.8)	286 (25.2)	493 (28.2)
Fatal	58 (9.5)	29 (2.6)	87 (5.0)
Unknown	41 (6.7)	92 (8.1)	133 (7.6)
Underlying renal disease			
No	549 (89.7)	1071 (94.4)	1620 (92.7)
Yes	63 (10.3)	64 (5.6)	127 (7.3)

[a]*SCARs* severe cutaneous adverse drug reactions

Table 2 Types of Allopurinol-Induced Severe Cutaneous Adverse Drug Reactions (SCARs) Reported and Time-to-Onset in Days (*n* = 612).

Types of SCARs	*n* (%)	Time-to-onset in days/[median (IQR)[a]]
Stevens–Johnson Syndrome (SJS)	352 (57.5)	19.0 (20.0)
SJS/Toxic epidermal necrolysis (SJS/TEN)	29 (4.7)	21.0 (16.5)
Toxic epidermal necrolysis (TEN)	64 (10.5)	15.0 (23.0)
Drug reaction with eosinophilia and systemic symptoms (DRESS)	157 (25.7)	28.0 (9.8)
Acute generalised exanthematous pustulosis (AGEP)	6 (1.0)	3.0 (17.5)
SJS and DRESS	4 (1.0)	28.5 (52.5)

[a]*IQR* interquartile range

Table 3 Risk Factors for Severe Cutaneous Adverse Drug Reactions (SCARs) Among All Allopurinol Reported Cases from Year 2000 to 2018 ($n=1747$).

Variables	Simple logistic regression		Multiple logistic regression	
	Crude odds ratio (95% CI)	*p* value	Adjusted odds ratio (95% CI)	*p* value
Age (years)				
<65	1	–	1	–
≥65	1.15 (0.94, 1.41)	0.164	1.31 (1.04, 1.64)	0.020
Gender				
Male	1	–	1	–
Female	1.62 (1.33, 1.98)	<0.001	1.54 (1.24, 1.93)	<0.001
Race				
Malay	1	–		
Chinese	1.19 (0.96, 1.48)	0.115		
Indian	0.98 (0.51, 1.91)	>0.950		
Others	0.67 (0.46, 0.99)	0.044		
Indication				
Registered indication	1	–	1	–
Unspecified hyperuricaemia	1.95 (1.39, 2.74)	<0.001	1.87 (1.29, 2.70)	0.001
Off-label indication	3.42 (2.27, 5.16)	<0.001	3.45 (2.20, 5.42)	<0.001
Allopurinol dose (milligram)				
<300 per day	1	–	1	–
≥300 per day	1.57 (1.28, 1.93)	<0.001	1.72 (1.38, 2.15)	<0.001
Time-to-onset (days)	1.00 (0.99, 1.00)	0.564		
Underlying renal disease				
No	1	–	1	–
Yes	1.92 (1.34, 2.76)	<0.001	2.02 (1.36, 3.00)	0.001

Forward LR Multiple Logistic model was applied

Model is fit with Hosmer–Lemeshow test $p=0.187$, Classification table = 67.8%, area under ROC curve = 65.1%

Allopurinol-Induced SCARs and Cases of Fatality

There were 58 SCARs-related fatality (9.4% of SCARs cases) comprising 24 SJS reports, 14 DRESS reports, 11 TEN reports, 8 SJS/TEN reports, and 1 AGEP case. Case-fatality rate for SJS/TEN was the highest at 27.5%. When fatality cases associated with allopurinol-induced SCARs were further analysed, we found that two factors were significantly associated i.e. age and type of SCARS. In terms of age, a patient who is 65 years old and above was 2.17 more likely to have a fatal outcome (95% CI 1.24, 3.80; $p=0.007$) compared to those below 65 years old. As for type of SCARs, fatality was 4.88 times more likely in patients diagnosed with SJS/TEN (95% CI 1.93, 12.31; $p=0.001$) and 2.86 times more likely in patients diagnosed with TEN (95% CI 1.31, 6.22; $p=0.008$) compared to those diagnosed with only SJS, respectively.

Discussion

Allopurinol hypersensitivity has been recognised since the 1980s [15]. Although newer research has shown the potential of pharmacogenetic screening and the Clinical Pharmacogenomics Implementation Consortium (CPIC) has recommended avoidance of allopurinol in those who are positive for *HLA-B*5801* [7], genetic screening is not common in most countries, including Malaysia. Thus, we sought to identify other non-genetic risk factors that would predict allopurinol-induced SCARs from the Malaysian pharmacovigilance database from year 2000 to 2018 and to assess its impact on fatality. Our findings show that significant predictors of allopurinol-induced SCARs were females, age of 65 years and above, allopurinol-prescribed dose of 300 mg and above daily, underlying renal disease, and allopurinol-prescribed indication of asymptomatic hyperuricaemia.

Patient and Drug-Related Predictors for Allopurinol-Induced SCARs

Despite having more allopurinol ADR reports from male patients in Malaysia, females were more likely to have SCARs compared to males in our study. Previous studies on allopurinol hypersensitivity and SCARs reported similar results [16–18]. The reason for the likelihood of females developing allopurinol-induced SCARs may also be due to a higher rate of prescribed medications compared to males [19]. Females were found to be more prone to ADRs than males [20, 21]. Patient's age, particularly those above 65 years, was one of the main risk factors for allopurinol-induced SCARS and fatality among SCARs cases. Elderly patients are more sensitive to pharmacokinetic changes, with a possibility of concomitant medications and are prone to liver or kidney impairment. Thus, as the pathogenesis of SCARs could be systemic, these group may be at risk of allopurinol-induced SCARs, especially elderly females, who are more likely to be diagnosed with gout [22].

Allopurinol-prescribed dose shows that ≥ 300 mg/day was associated with a higher risk of SCARs. A similar result was reported in a previous EuroSCAR study that a higher allopurinol dose was associated with a higher risk for SJS or TEN, although a lower daily dose (≥ 200 mg/day) was reported as compared to our study [23].

Allopurinol-prescribed dose is also closely related to another factor identified which is underlying renal disease. A Japanese study concluded that the approved allopurinol dosage range of 200 to 300 mg daily may be too high for patients with renal dysfunction [24]. They also found that a daily dose of 100 to 200 mg may be enough to obtain therapeutic serum oxypurinol concentrations in most Japanese patients. In our study, we found that underlying renal disease was the strongest risk factors for allopurinol-induced SCARs. Patients with underlying renal disease were two times more likely to have SCARs. Previous studies also found a significant association between poor renal function and the increased risk of allopurinol-induced SCARs [25, 26].

Singer and Wallace [15] observed that patients who have gout or hyperuricaemia along with renal insufficiency are at a greater risk of developing severe side effects from treatment with allopurinol. It has been suggested that oxypurinol could induce SCARs as it can cause dose-dependent T-cell response in vitro [26]. Since oxypurinol is mainly excreted through the kidney, reduced renal function was linked to delayed clearance of plasma oxypurinol [25]. In healthy patients, the half-life of oxypurinol is 12–30 h. However, in renal impairment, plasma oxypurinol remained detectable 2 weeks after allopurinol withdrawal [14]. The increased plasma level of oxypurinol was linked to high mortality of allopurinol-induced SJS/TEN [25]. Therefore, measurement of oxypurinol may complement diagnosis as another alternative to achieve effective therapeutic dose and to possibly avoid adverse reactions.

Genderwise, it was interesting to note that elderly females were more associated with allopurinol-induced SCARs compared to males, whereas underlying kidney disease which is our strongest predictor, is usually more common in males. Gender differences related to renal disorders have been widely discussed in other studies [27, 28]. However, we could not further analyse the association as underlying kidney disease reported in our study included variable terms of chronic kidney disease, renal impairment, and end-stage renal disease based on spontaneous ADR reports. Careful monitoring in allopurinol-prescribed elderly females is advocated while awaiting further research.

Reported Use with Allopurinol-Induced SCARs

Allopurinol-prescribed indications in our study were further classified as registered, off-label, unspecified, or unknown. In Malaysia, asymptomatic hyperuricaemia, uncomplicated gout, and acute gouty attacks are not indicated for allopurinol therapy [3]. We found that patients prescribed allopurinol for unspecified hyperuricaemia and off-label indications were more likely to report SCARs compared to allopurinol prescribed for registered indications. Campion et al. [29] studied rates for a trigger of gouty arthritis in a cohort of 2046 healthy men for 15 years with serial examinations and measurement of urate levels. The strongest predictors of gout were age, body mass index, hypertension, cholesterol level, and alcohol intake. However, none of the variables retained independent predictive power when serum urate level became a factor which showed that serum urate level was not a predictor of gout [29]. In Malaysian public hospitals, uric acid testing has been removed from routine renal profile screening in year 2011. Among the reasons were to avoid unnecessary treatment with allopurinol for asymptomatic hyperuricaemia and expose patients to the drug and its risks. Healthcare professionals need to be aware of the reasons when prescribing allopurinol. It is essential to have strict treatment protocols for allopurinol to avoid this preventable ADR.

Allopurinol-Induced SCARs and Cases of Fatality

As we sought to assess the impact of allopurinol reported cases on fatality, our study identified 58 SCARs-related fatality (9.4%). Fatality was found to be significantly impacted by age and the type of SCARs. Although these results must be interpreted with caution, our findings were aligned with other studies on SCARs-related mortality. A Thai study identified that the overall mortality rate of allopurinol-induced SCAR was 11.39% and a higher mortality rate

was observed in elderly women [17]. Our results concur with Yang et al. [16] who found that patients aged 60 years or older were associated with increased risk of hypersensitivity-related mortality. Age of 40 years old and above was deemed one of the risk factors for TEN-specific severity of illness score (SCORTEN) developed by Fouchard et al. [30]. With regard to type of allopurinol-induced SCARs, SJS caused the highest number of deaths, followed by DRESS and TEN. Based on our study, an allopurinol-induced SCAR could occur within the range of 15 days (TEN) to 28 days (DRESS). Thus, any new patients or those initiated on a higher dose should be closely monitored during this period and cautioned of the risks. A few studies have shown that SCARs tend to occur within the first 180 days of treatment [31, 32]. What remains unknown is the impact of these SCARs in the lives of patients who survived the ordeal. A qualitative survey among SCAR-experienced patients in the United Kingdom found that they were fearful and now avoided medicines altogether [33]. Better communication post-recovery by healthcare providers is also advocated for SCAR-experienced patients as elderly patients may also take more medications due to other comorbidities.

Strengths and Limitations of A Spontaneous ADR Reporting System

Our study was based on 19 years of national ADR reports with allopurinol as one of the highest reported in Malaysia and worldwide [11]. Although we selected all allopurinol ADR reports, the findings are subjected to the drawbacks of a spontaneous reporting system such as under-reporting and reporting bias [34]. The analysis was carried out based on voluntary reports, without intervention. Thus, we could not assess cardiovascular comorbidities or concomitant medications, due to incomplete reporting. Further improvements in the quality of reporting ADRs by healthcare professionals can contribute to signal detection not just for allopurinol but for also other drugs. Our findings also concur with the factors identified by other studies [16, 35, 36] which also used reported databases for allopurinol patients.

Practical Implications and Future Consideration

Additionally, our study showed that the majority of the allopurinol-induced SCAR cases were from the Malay population. It would be interesting to see whether the Malay population also possessed the susceptible *HLA-B*58:01* allele which have not been studied elsewhere. Perhaps pharmacogenetic screening can be initiated in this susceptible group identified in this study as high-risk patients, before starting allopurinol therapy. Genetic testing for *HLA-B*58:01* before allopurinol administration is considered a potentially cost-effective intervention in Thailand [37]. Further studies could also utilise these data to assess the economic impact of SCARs and its mortality on our healthcare resources.

Conclusions

Malaysian pharmacovigilance data show that risk factors for allopurinol-induced SCARs include elderly females, patients with underlying renal disease, and those prescribed allopurinol doses above 300 mg. These patients require close monitoring. Risk factors associated with fatality were older age and the type of SCARs. Allopurinol-induced SCARs can be considered a preventable ADR. Increased efforts need to be taken for vigilance and to educate patients on the signs and symptoms of allopurinol hypersensitivity to prevent further complications.

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Author Contribution

NMA, LSC, and VH conceived and designed the study. WWK, NMA, and LSC extracted and reviewed the data. LSC, YHS, and VH were involved in data analysis and interpretation. LSC and YHS drafted the manuscript. VH revised the manuscript. All authors read and approved the final manuscript for submission.

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Conflict of interest

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