Severe cutaneous adverse reactions: A 5-year retrospective study at Hospital Melaka, Malaysia, from December 2014 to February 2020

Chiaw Ting Tee, MRCP(UK), Noor Hairiza Binti Abdullah, MD(UNIBRAW), Punitha Kristummoonthy, MD(MMA), Choon Sian Lee, AdvMDerm(UKM)

Department of Dermatology, Hospital Melaka, Malaysia

ABSTRACT

Introduction: Severe cutaneous adverse reactions (SCARs) are potentially lethal adverse drug reactions that involve the skin, mucous membranes, and internal organs, resulting in disability. SCARs include drug-induced epidermal necrolysis, which is Steven Johnson syndrome (SJS)/ Steven Johnson syndrome and toxic epidermal necrolysis overlap (SJS-TEN overlap)/ toxic epidermal necrolysis (TEN), drug reaction with eosinophilia and systemic symptoms (DRESS), acute generalised exanthematous pustulosis (AGEP), generalised bullous fixed drug eruption (GBFDE), and acute erythroderma. Awareness of local epidemiology of SCARs plays an important role in prescribing practices by healthcare provider. Recognition of SCARs enables the offending drug to be withdrawn immediately, which is the definitive treatment of SCARs.

Materials and Methods: This is a retrospective study reviewing SCAR cases reported to the Malaysian Adverse Drug Reactions Advisory Committee (MADRAC) registry at the Department of Dermatology, Hospital Melaka, for 5 years and 3 months from December 2014 to February 2020.

Results: A total of 41 SCARs cases were identified over the study duration. The incidence rate was 0.18%. All 41 cases require hospitalisations, with four cases (9.8%) managed in ICU and one mortality (2.4%) due to SJS-related complication. One patient had two episodes of SCARs. There were 22 male patients and 18 female patients. The majority were Malays (33, 80.5%), followed by Chinese (7, 17.1%) and Indonesian (1, 2.4%). There was no Indian patient with SCARs in this study. The mean age of patients was 47.2±17 years. Drug-induced epidermal necrolysis was the commonest type of SCARs (63.4%), and out of this, SJS accounted for the majority of cases (48.8%). Antibiotic was the main group of offending medication in this SCAR study (29.3%). The top five individual causative drugs of SCARs in sequence include allopurinol, phenytoin, carbamazepine, co-amoxiclav, and cephalexin. Allopurinol was the commonest culprit drug for drug-induced epidermal necrolysis and DRESS, phenytoin for acute erythroderma, and co-amoxiclav for AGEP.

Conclusion: SJS was the most common manifestation and Allopurinol was the commonest culprit drug for SCAR cases in our cohort.

KEYWORDS:
Severe cutaneous adverse reactions, Allopurinol, Drug-induced epidermal necrolysis

INTRODUCTION

Cutaneous adverse drug reaction (cADR) is defined as undesirable change in the structure or function of the skin, its appendages, or mucous membranes caused by a drug. cADRs are classified into severe and non-severe reactions. Severe cutaneous adverse reactions (SCARs) are a group of potentially lethal adverse drug reactions that involve the skin, mucous membranes, and internal organs, which results in persistent or significant disability, requiring hospital admission, intensive care, or specific interventional treatment. SCARs encompassed (1) drug-induced epidermal necrolysis (Steven Johnson syndrome [SJS], toxic epidermal necrolysis [TEN], SJS-TEN overlap), (2) drug reaction with eosinophilia and systemic Symptoms (DRESS), (3) acute generalised exanthematous pustulosis (AGEP), (4) generalised bullous fixed drug eruption (GBFDE), and (5) drug-induced acute erythroderma.[1,2] Each SCAR has its own characteristic cutaneous presentations, causative drugs, clinical courses, and treatment modalities.

SCARs can occur in patients of any age, ranging from children to elderly. Medications are the leading trigger of SCARs. Antibiotics, anticonvulsants, and non-steroidal anti-inflammatory drugs (NSAIDS) are the common groups of drugs responsible for SCARs.[1] Hence, the decision to initiate any treatment should be justified to prevent or reduce unnecessary morbidity or mortality. It is very important to acquire knowledge on SCARs because it implies great impact on morbidity, mortality, and hospital costs. Therefore, treating physicians should promptly recognise SCARs through the identification of their characteristic clinical features, so that the offending drug is withdrawn immediately and supportive therapies are administered.

SCARs are diagnosed mainly based on clinical history, physical cutaneous finding, blood investigation, and skin biopsy at lesser extent. Hospital-based studies are expected to detect more cases of SCARs, as they are referral centres for close monitoring and management of SCARs that can cause fatalities. Various hospitals worldwide reported the characteristics of SCARs where the data were obtained mainly from respective dermatology clinics. Awareness of local

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Corresponding Author: Chiaw Ting Tee
Email: teechiawting@hotmail.com

epidemiology of SCARs play an important role in prescribing practices by healthcare provider. Hence, a retrospective review of all patients referred to the Department of Dermatology, Hospital Melaka, Malaysia, from December 2014 to February 2020 ,was carried out to determine the local epidemiological patterns and the common drugs implicated.

MATERIALS AND METHODS

This is a retrospective study comprising 5-year and 3-month data (December 2014 to February 2020) collected from the Malaysian Adverse Drug Reactions Advisory Committee (MADRAC) registry, and dermatology records from the Department of Dermatology, Hospital Melaka, Malaysia.

Drug-induced epidermal necrolysis is characterised by extensive necrosis and detachment of the epidermis, with two or more mucous membrane involvement. For SJS, the epidermal detachment is <10% of body surface area (BSA), TEN involves detachment of >30%, and SJS/TEN overlap described patients with epidermal detachment of 10-30% BSA.[1] DRESS is diagnosed using the European Registry of Severe Cutaneous Adverse Reaction (RegiSCAR) diagnostic criteria. The criteria include hospitalised patient with acute rash, suspicion of a drug-related reaction, with three out of these systemic features: fever of 38°C, lymphadenopathy involving at least two sites, involvement of at least one internal organ, and haematological abnormalities, such as eosinophilia.[3] AGEP is characterised by numerous small, non-follicular sterile pustules, arising from erythematous base, with high fever and raised neutrophil count. The diagnosis of AGEP is further confirmed histologically, in which spongiform subcorneal and/or intraepidermal pustules with papillary oedema is looked for.[3] GBFDE is defined as fixed drug eruption lesions with widespread blisters and erosions involving more than 10% BSA in at least three out of six sites (head and neck, anterior trunk, back, upper limbs, lower limbs, and genitalia).[1] Drug-induced acute erythroderma is characterised by generalised skin redness affecting more than 90% of the BSA.[3]

All cases with SCARs were identified from MADRAC registry at the Department of Dermatology, Hospital Melaka, and only those labelled as definite, probable, and possible cADR based on Naranjo Classification by the dermatologist were selected. Data on patient demography, clinical patterns, causative drugs, treatment, and clinical outcomes were collected from patients' case notes. Patients' files with incomplete data entry were excluded from analysis.

Data were processed using Microsoft excel XL, SPSS statistics software version 23.0. Numerical variables were described using mean ± standard deviation (SD). Nominal variables were described using frequencies and percentages. Statistical significance was taken at the $p<0.05$ level. Ministry of Health Malaysia Research Ethics Committee (MREC)'s approval was obtained prior to the commencement of study.

RESULTS

A total of 41 SCAR cases were identified over the study duration of 5 years and 3 months. Forty-one cases involved 40 patients, in which one of the patients developed SCARs twice during the study period. There was a male preponderance with 23 cases involving male patients and 18 cases involving female patients. Male preponderance was seen in AGEP as well as acute erythroderma, with the male to female ratio of 4:1 and 7:1, respectively. In contrast, there were more female patients who developed SJS/TEN/SJS-TEN overlap than male patients, with the female to male ratio of 15: 11. However, the gender ratio was equal (1:1) in DRESS.

The majority of patients were Malay, 33 cases (80.5%), followed by Chinese, 7 cases (17.1%), and 1 Indonesian (2.4%). There was no Indian patient with SCARs detected over this study duration in Hospital Melaka. The racial distribution of patients in our department comprised of 64.5% Malay, 26.4% Chinese, 7.5% Indian, and 1.5% from others. SCARs can occur in any age, ranging from children to elderly. The age of SCAR patients in this study ranged from 17 to 77 years, with the mean age of 47.2 years (Table I).

Most of the patients who developed SCARs have underlying comorbidities, with 38 out of 41 cases (92.7%). There were five patients with underlying retroviral disease (12.2%), three with renal impairment (7.3%), and one with underlying malignancy (2.4%). Comorbidity is the main factor leading to polypharmacy. Thirty-six out of 41 cases involved co-administration of medication for the underlying medical condition. This study revealed that almost a quarter of SCAR cases (10 out of 41 cases, 24.4%) occur in patients with prior history of allergy, either to medication or to food. All 41 cases (100%) require hospitalisation, in which four out of 41 cases (9.8%) were managed in intensive care unit. Unfortunately, there was one mortality case due to SJS-related complication.

SJS/TEN/SJS-TEN overlap accounted for the majority of SCAR cases in this retrospective study, as there were 26 cases (63.4%). This was followed by acute erythroderma, eight cases (19.5%), as the second highest SCARs in this study. There were five AGEP cases (12.2%) and two cases of DRESS (4.9%). None of the SCARs was attributed to GBFDE (Figure 1).

Antibiotics were the main causative agents in this SCAR study, as there were 12 cases in total (29.3%). This was followed by 10 cases caused by allopurinol (24.4%) and nine cases attributed to anticonvulsant (22.0%). NSAIDs and antiretroviral (ARV) accounted for one (2.4%) and two cases (4.9%), respectively (Figure 2).

In addition to allopurinol (10 cases, 24.4%), the other top five individual causative drugs in this SCAR study include phenytoin, carbamazepine, co-amoxiclav, and cephalexin (Figure 3). Both phenytoin and carbamazepine resulted in four cases each, which contributed to 9.8% of total cases each, while three cases were related to co-amoxiclav (7.3%) and two cases by cephalexin (4.9%). Allopurinol was the commonest causative drug for SJS/TEN/SJS-TEN overlap and DRESS in this study (six cases of SJS; two cases of TEN; two cases of DRESS), whereas co-amoxiclav was the commonest causative agent for AGEP while phenytoin being the top causative medication in acute erythroderma.

Table I: Demographic and clinical data

Characteristics	n = 41
Male: Female ratio	1.28: 1
Mean age in years (range)	47.2 (17-77)
Ethnicity –	
Malay	33 (80.5%)
Chinese	7 (17.1%)
Indian	0 (0.0%)
Others	1 (2.4%)
Patients with comorbidity	38 (92.7%)
Patients with underlying malignancy	1 (2.4%)
Patients with underlying HIV	5 (12.2%)
Patients with renal impairment	3 (7.3%)
Patients with history of allergy	10 (24.4%)
Patients with polypharmacy	36 (87.8%)
Patients hospitalised	41 (100.0%)
Mortality at acute event	1 (2.4%)
Number of ICU/HDW admission	4 (9.8%)

Table II: A comparison of clinicoepidemiological studies on SCARs in various hospitals, Malaysia

	Melaka (Dec 2014–Feb 2020)	Klang (2009–2013)[4]	Kuantan (2013–2016)[5]	Penang (2006–2015)[1]
Duration of study	5 years 3 months	5 years	4 years	10 years
Total SCAR cases	41	33	25	189
Male: Female ratio	1.28 : 1	1.38 : 1	1 : 1.27	1 : 1.20
Ethnicity	Malay 80.5% Chinese 17.1% Indian 0.0% Others 2.4%	Malay 67% Chinese 24% Indian 6% Others 3%	Malay 64% Chinese 24% Indian 8% Others 4%	Malay 49% Chinese 38% Indian 11%
Mean age	47.2 years	42.8 years	53.7 years	45 years
Age range	17–77 years	7–81 years	4–92 years	2–87 years
The most common SCAR	SJS (48.8%)	SJS (75.8%)	SJS (60%)	SJS (55%)
The most common group of offending medication	Antibiotics (29.3%)	Allopurinol (33.3%)	Antibiotics (44.0%)	Antibiotics (33.3%)
The most common individual causative drug	Allopurinol	Allopurinol	Allopurinol	Allopurinol
Mortality rate	2.4%	9.1%	8.0%	5.8%

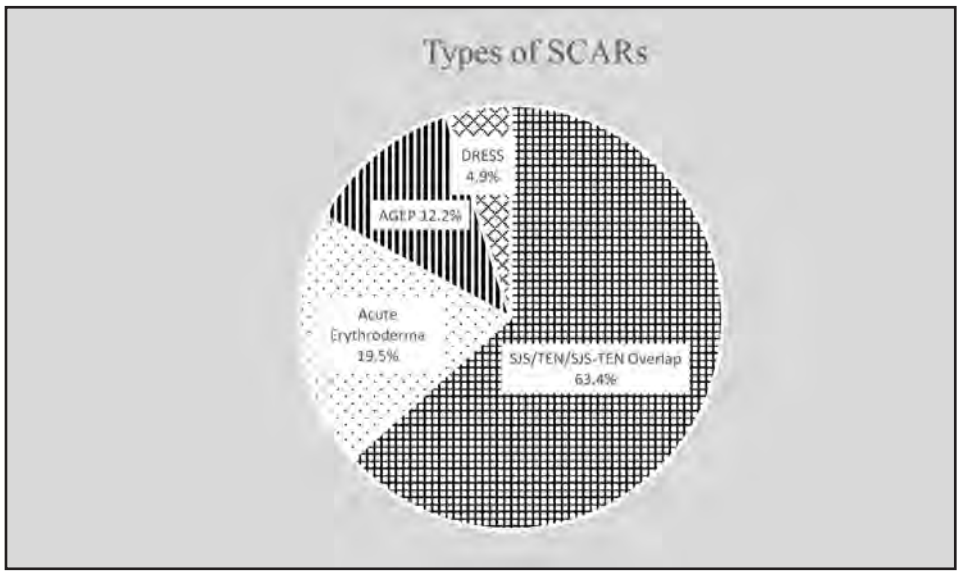

Fig. 1: Types of SCARs

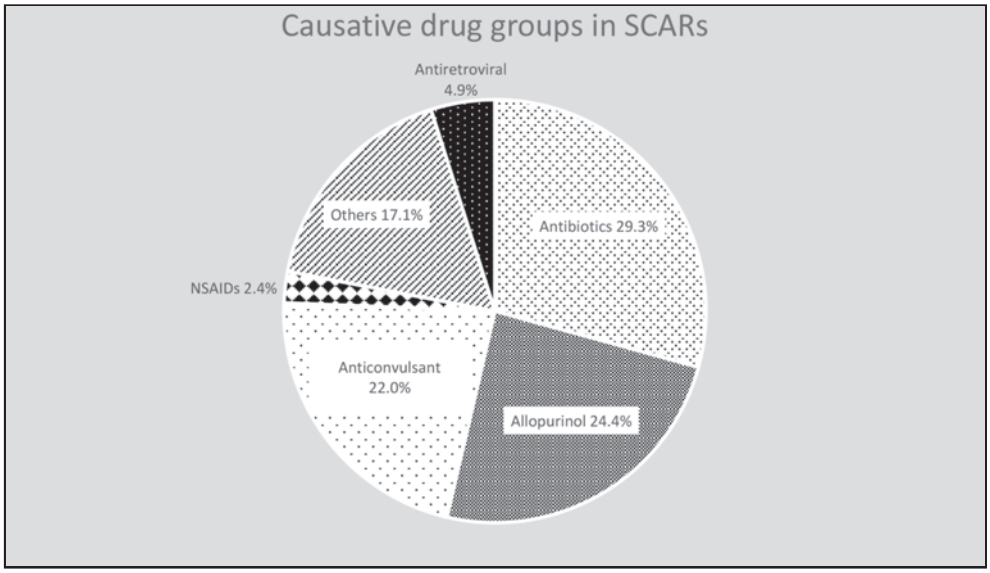

Fig. 2: Causative drug groups in SCARs

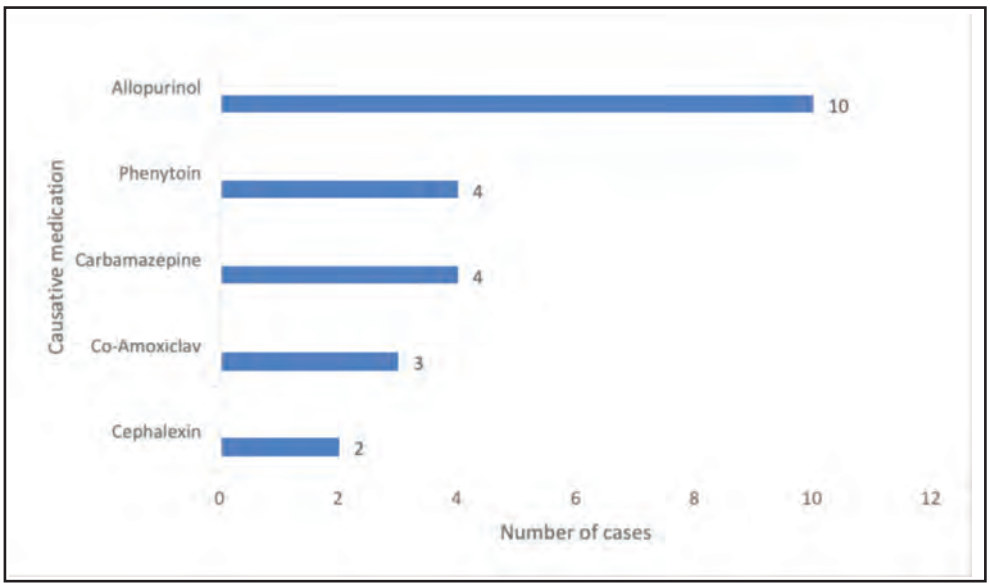

Fig. 3: Top five individual causative drugs

Co-amoxiclav resulting in two cases of AGEP and one case of SJS-TEN overlaps. All four SCAR cases due to phenytoin were acute erythroderma, while all four cases due to carbamazepine were SJS. Two SCAR cases secondary to cephalexin were SJS as well. There was an increasing trend of prescribing allopurinol from year 2014 to 2017, followed by a decline during the subsequent years. Four patients were prescribed with allopurinol for gouty arthritis, and three were prescribed for asymptomatic hyperuricemia, while for the remaining three patients, indication was not stated.

DISCUSSION

Patterns of SCARs and their causative drugs vary among the different populations. Understanding of local epidemiology of SCARs play an important role in prescribing practices. Out of the 260 cases of cADRs referred to the Department of Dermatology, Hospital Melaka, from December 2014 to February 2020, 41(15.8%) were SCARs. There were 22,474 new cases seen during that period, yielding an incidence rate of 0.18%.

The mean age of patients in this study was 47.2 years, with patients' age ranging from 17 to 77 years. There was no

paediatric patient with SCARs reported in this study, although paediatric population was not excluded in the study. This is in contrast with studies done in Klang, Kuantan, and Penang Hospital, with the youngest age groups of 7, 4, and 2, respectively. SCARs in children are not common but potentially serious.[1,4-6] SCARs are more commonly seen with increasing age, as this can be attributed to the associated comorbidities requiring polypharmacy. Almost 92.7% of our cases have comorbidities with 43.9% of patients taking at least one or two concomitant medications. This study showed slight male preponderance with the male to female ratio of 1.28:1. This is similar to the Klang study with male to female ratio of 1.38:1.[4] However, both studies in Kuantan and Penang showed female preponderance, in which the male to female ratios were 1:1.27 and 1:1.2, respectively.[1,5]

One of our patients was diagnosed to have SCARs twice within the study duration. Both the incidence took place in 2017, with the time frame of five months apart. This was a patient with retroviral disease, who developed TEN due to nevirapine, followed by SJS secondary to dapsone five months later. This highlights that cADRs and SCARs are common among patients with retroviral disease.[7] Genetic factors can predispose an individual to SCARs according to pharmacogenomic study. Genetic markers enable elucidation of the pathogenesis of SCARs, as well as screening of susceptible subjects.[8] The HLA alleles associated with hypersensitivity reactions to nevirapine also differ by ethnicity. In Thailand, hypersensitivity to nevirapine is associated with HLA-B*35:05.[9] HLA-B*13:01 is associated with SCARs secondary to dapsone in Asians.[8] A pharmacogenomic study needs to be considered in high-risk patients, especially those with recurrent incidence of SCARs.

Despite the Ministry of Health's effort of changing prescribing category for allopurinol from B (can be prescribed by medical officers) to A/KK (can only be prescribed by consultants/specialists/family medicine specialists) in 2011, allopurinol remains the commonest causative drug for SCARs in the study conducted in Kuantan, Malaysia, from 2013 to 2016.[5] The similar result was obtained in our study cohort, with allopurinol being the commonest drug in total SCARs cases (24.4%), as well as in SJS/TEN/SJS-TEN overlap and DRESS. Continuous reminder of judicious prescribing allopurinol with justified indication is emphasised from time to time, in order to reduce the incidence of SCARs induced by allopurinol. HLA-B*58:01 allele is an important genetic marker in allopurinol-induced SCARs. This is supported by a local study, which revealed strong association between HLA-B*58:01 and allopurinol induced SCARs in multi-ethnic Malaysian population, particularly in Chinese and Malays.[10] Pre-emptive genetic screening should be considered when commencement of allopurinol is absolutely indicated.

In Malaysia, SJS was reported as the most common manifestation of SCARs according to studies done in tertiary hospital in Penang and Kuantan.[1,5] This is consistent with our study, in which SJS was the most common manifestation of SCARs. Drug-induced epidermal necrolysis, which include SJS/TEN/SJS-TEN overlap, accounts for 63.4% of SCARs, and of this, SJS 48.8%, TEN 9.8%, and SJS-TEN overlap 4.9%. Antibiotics were the predominant group of drugs, which contributed to 29.3% of SCARs in our study. This is comparable to 30.3% in Klang Hospital, 33.3% in Penang, and 44.0% in Kuantan studies. This reminds us of more judicious antibiotic usage in the future.[1,4-5]

Contrastingly, a study from Brazil revealed DRESS as the most frequent SCAR presentation and the drugs most frequently involved were anticonvulsants.[11] This discrepancy can be either due to different prescribing practices or genetic predisposition. Although allopurinol was reported as the commonest causative agent for SJS and TEN in Malaysia studies, a study from Nigeria revealed antiretroviral as the commonest offending drug of SJS and TEN, with nevirapine being the most widely implicated drugs.[12]

There was one mortality case (2.4%) in our study, due to SJS-related complication. Mortality rate for studies done in Klang Hospital was 9.1%, in Kuantan Hospital 8.0%, and in Penang 5.8%.[1,4-5] Early drug withdrawal is mandatory in all SCARs. Physicians' knowledge is essential to the improvement of diagnosis and management, as well as prevention of long-term sequelae.

LIMITATION OF THE STUDY

This study is limited by its retrospective design.

CONCLUSION

SJS was the most common manifestation, and allopurinol was the commonest culprit drug for SCAR cases in our cohort. Medicines are to be prescribed when absolutely indicated.

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CONFLICT OF INTEREST

There is no conflict of interest related to this study.

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