A 10-years retrospective study on Severe Cutaneous Adverse Reactions (SCARs) in a tertiary hospital in Penang, Malaysia

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ABSTRACT

Introduction: Severe cutaneous adverse drug reactions (SCARs) are not uncommon and potentially life-threatening. Our objective is to study the patient characteristics, the pattern of implicated drugs and treatment outcome among patients with SCARs.

Methods: A 10-year retrospective analysis of SCARs cases in Penang General Hospital was carried out from January 2006 to December 2015. Data collection is based on the Malaysian Adverse Drug Reactions Advisory Committee registry and dermatology clinic records.

Results: A total of 189 cases of SCARs were encountered (F:M ratio; 1.2:1.0; mean age of 45 year). The commonest manifestation was Stevens-Johnson Syndrome [SJS] (55.0%), followed by toxic epidermal necrolysis [TEN] (23.8%), drug rash with eosinophilia and systemic symptoms [DRESS] (12.7%), acute generalised exanthematous pustulosis [AGEP] (4.8%), SJS/TEN overlap syndrome (2.6%) and generalised bullous fixed drug eruptions [GBFDE] (1.1%). Mean time to onset for TEN/SJS/Overlap syndrome was 10.5±13 days; AGEP, three days; GBFDE, 2.5±0.7 days, and DRESS, 29.4±5.7 days. The most common drugs implicated were antibiotics (33.3%), followed by allopurinol (18.9%) and anticonvulsant (18.4%). Out of 154 cases of SJS/TEN/overlap syndrome, allopurinol was the commonest causative agents (20.1%). In DRESS, allopurinol accounts for 45.8% of the cases. The mortality rate in SJS, TEN and DRESS were 1.9%, 13.3% and 12.5% respectively. No mortality was observed in AGEP and GBFDE.

Conclusion: The commonest manifestations of SCARs in our setting were SJS, TEN and DRESS. Allopurinol was the most common culprit. Thus, judicious allopurinol use is advocated and pre-emptive genetic screening for HLA-B *5801 should be considered.

KEY WORDS:
Stevens-Johnson Syndrome, Toxic epidermal necrolysis, DRESS, GBFDE, AGEP

INTRODUCTION

Cutaneous adverse drug reactions (CADRs) is one of the more common adverse drug reactions seen in hospitalised patients. It constitutes 10 to 30% of all reported adverse drug reactions.[1] Clinical presentation ranges from mild reactions like a maculopapular rash to severe, life-threatening conditions such as toxic epidermal necrolysis (TEN). Hospitalisations from drug reactions are as high as 5 to 8%, with CADRs accounting for 2% of these admissions.[2] According to the World Health Organization (WHO), severe cutaneous adverse reactions (SCARs) refers to those requiring hospitalisation, with significant morbidity and mortality or are life-threatening.[3] These encompass Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), acute generalised exanthematous pustulosis (AGEP), generalised bullous fixed drug eruptions (GBFDE) and drug rash with eosinophilia and systemic symptoms (DRESS). In Singapore, SCARs constitute 5 to14% of CADR.[4] International studies have shown that the overall mortality rate among patients with SJS and TEN are 10% and 30% respectively,[5] while delayed mortality is seen in 5 to 10% in the following weeks.[6] Mortality rate for DRESS is estimated at 10%.[7]

The prevalence and patterns of SCARs differ greatly between different populations and geographic distribution. The incidence of TEN in Singapore is estimated to be at least 1.4 cases/million population,[8] while the incidence in United State is 0.5 cases/million population.[9] Other authors revealed that SJS had an annual incidence of 1.2 to 6 cases per million people which is a 4-fold higher than the incidence of TEN, 0.4 to 1.2 cases per million people.[9,10] DRESS, the other severe idiosyncratic drug reaction associated with multi-organ involvement has an incidence of 1/1000 to 1/10,000 drug exposures.[11]

EuroSCAR studies have reported that the majority of the reactions are attributed to a group of high-risk drugs such as allopurinol, carbamazepine, phenytoin, lamotrigine, oxicam nonsteroidal anti-inflammatory drugs, sulfonamide antibiotics and nevirapine. South-East Asian data also showed similar causative agents.[12] Unfortunately, local Malaysian data is lacking.

The objective of this study is to study the patient characteristics, implicated drug patterns and treatment outcome among patients with SCARs. This would enable us to better understand the disease pattern, guide us in giving better patient care as well as the judicious medication prescription in the future.

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Table I: Drugs implicated in SCAR

Drug	TOTAL	Percentage (%)
ANTIBIOTICS	**77**	**33.7**
Penicillin group (Amoxycillin 9; Ampicillin 3; cloxacillin 3; penicillin 3; co-amoxiclav 5, ampicillin/sulbactam 4)	27	
Sulphonamides (Bactrim 21; Sulfadoxine/pyrimethamine 5; Dapsone 1)	27	
Cephalosporins (Ceftriazone 4; Cefazolin 1; cefoperazone 1; ceftazidime 1; cephalexin 1)	8	
Quinolone (Ciprofloxacin 2, moxifloxacin 2)	4	
Tetracyclines (tetracycline 2; Doxycycline 1)	3	
Anti-tuberculosis (ethambutol 1; isoniazid 1; rifampicin 1; pyrazinamide 1)	4	
Others (Erythromycin 1; Clindamycin 2; Gentamicin 1)	4	
ANTICONVULSANTS	**42**	**18.4**
Phenytoin	22	
Carbamazepine	17	
Lamotrigine	3	
ANTIGOUT	**43**	**18.9**
Allopurinol	43	
NSAIDS/ANALGESIC	**34**	**14.9**
NSAIDS (Diclofenac 5; Etoricoxib 1; Ibuprofen 2; Mefenamic acid 8; Aspirin 1; Piroxicam 1; NSAIDS 5)	23	
Paracetamol	10	
Tramadol	1	
ANTIRHEUMATIC	**2**	**0.9**
Leflunamide	1	
Sulfasalazine	1	
ANTIVIRAL	**12**	**5.3**
Efavirenz 3; Lamivudine 2; Nevirapine 4; Stavudine 3	12	
ANTIHYPERTENSIVES	**5**	**2.2**
Amlodipine	1	
Diltiazem	2	
Frusemide	2	
Others	**13**	**5.7**
Carbimazole 1; Cetirizine 2; Omeprazole 4; Ranitidine 2; Recormon 1; Traditional medication 3)		
TOTAL	**228**	**100**

Table II: Interval between drug administration and onset of symptoms

	Epidermal Necrolysis	AGEP	DRESS	GBFDE
Mean Time to Onset (Days)	12.5	3	29.4	2.5

MATERIALS AND METHODS

Data collection

This is a 10-year retrospective analysis of SCARs cases seen in Penang Hospital, Malaysia from January 2006 to December 2015. Only severe types of CADR, such as SJS, TEN, SJS/TEN overlap syndrome, AGEP, DRESS and GBFDE were included. SJS is defined as an epidermal detachment of <10% body surface area (BSA), while SJS/TEN overlap syndrome involved epidermal detachment of 10 to 30%. A detachment of more than 30% BSA is considered as TEN.[3] AGEP is an acute febrile eruption characterised by numerous small, nonfollicular pustules, arising from large areas of the edematous erythematous base.[3] There are three proposed diagnostic criteria for DRESS, we opted for the RegiSCAR criteria which include hospitalised patients with reaction suspected to be drug-related with at least three out of these findings: fever >38°C, lymphadenopathy involved at least two sites, internal organ and haematological abnormalities. GBFDE is defined as typically fixed drug eruption (FDE) 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).[13]

We collected our data from MADRAC (Malaysian Adverse Drug Reactions Advisory Committee) registry and dermatology clinic records (2006-2015). Information on patient demography, type of adverse reactions, causative agents, time to onset, treatment modalities and disease outcome was obtained and analysed.

Statistical analysis

A descriptive statistical analysis was conducted using Statistical Package for the Social Sciences (SPSS 22.0, IBM, USA). The normally distributed continuous variables are summarized in mean and standard deviation (SD) while the non-normally distributed are expressed as median and inter quartile range (IQR). For categorical variables, frequencies and percentages were tabulated. The significance level was set at $P<0.05$. Approval from Ministry of Health Malaysia Research Ethics Committee (MREC) was obtained.

RESULTS

Demographics

A total of 189 cases of SCARs were identified over the past 10 years. With a total of 614,747 hospital admissions and 46,708 clinic consultations, SCARs account for 0.03% (0.3/1000) of total hospital admission and 0.42% of dermatology clinic attendance respectively. The majority of patients were Malays (49%, n=93) followed by Chinese (38%, n=71) and Indian (11%, n=20). There was a female preponderance with a female to male ratio of 1.2:1.0. However, a male preponderance was seen in DRESS and AGEP, with a male to female ratio of 1:0.6 and 1:0.8

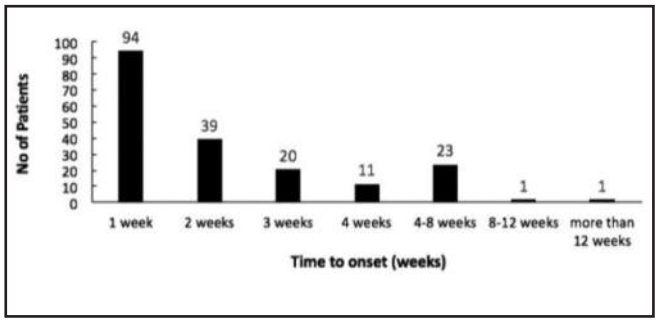

Fig. 1: Interval between drug administration and inset if symptoms.

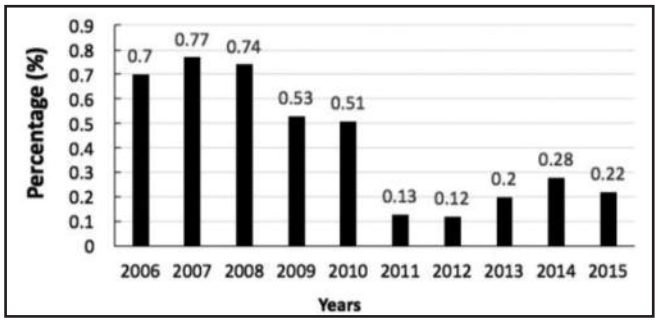

Fig. 2: Percentage of SCARs in dermatology clinic attendance.

respectively. (p=0.065). Patient's age ranged from 2 to 87 years old, with the mean at 45 years old. There was an increase in SCARs with age.

Reaction Pattern of SCARs

The commonest reaction pattern of SCARs in our cohort was epidermal necrolysis (81.4%, n=154), followed by DRESS (12.7%, n=24), AGEP (4.8%, n=9) and GBFDE (1.1%, n=2). Epidermal necrolysis included SJS, 55.0% (n=104), SJS/TEN overlap syndrome, 2.6% (n=5) and
TEN 23.8% (n=45).

Implicated Drugs

A total of 228 drugs were identified. They were classified broadly into eight groups (Table I). Antibiotics were the most common at 33.7%, followed by anti-gout (Allopurinol) and anticonvulsant at 18.9% and 18.4% respectively. NSAIDS contributed 10% of SCARs. Cotrimoxazole (n=21), amoxicillin (n=9) and augmentin (n=5) were the commonest implicated antibiotics. Aromatic anticonvulsants like phenytoin (n=22) and carbamazepine (n=17) remained the most common anticonvulsants causing SCARs. Individually, allopurinol was the most prevalent drug implicated (18.9%, n=43), responsible for 20.8% of SJS/TEN (31 out of 149), 46% of DRESS (11 out of 24) and 11% of AGEP (1 out of 9).

Interval between the drug administration and onset of symptoms

The time frame between drug administration and symptom onset was highly variable. The latency periods based on different types of SCARs are summarised in Tables II. Almost 99% of SCARs occurred within the first eight weeks of drug administration with half of them developing adverse reactions within the first week of drug administration. (Figure 1). DRESS had the longest interval, at 29.4 days.

Treatment

All patients received symptomatic treatment and this included withholding the offending drugs and prescription of topical medication as well as an oral antihistamine. Approximately 41.3% (n=78) required systemic treatment of either systemic corticosteroid or intravenous immunoglobulin. Of these, systemic corticosteroid was prescribed in six cases of SJS (5.8%), four TEN (8.9%), 21 DRESS (87.5%), five AGEP (55.6%) and two cases of GBFDE (100%). On the other hand, intravenous immunoglobulin was only used for epidermal necrolysis [6 SJS (5.8%); one SJS/TEN (0.5%); 33 TEN (73.3%)].

Mortality

The total mortality of SCARs in this study was 5.8% (n=11), contributed by both epidermal necrolysis and DRESS. TEN had the highest mortality rate at 13.3% (6 out of 45), followed by DRESS 12.5% (3 out of 24) and SJS 1.9% (2 out of 104). Allopurinol was responsible for a total of 5 mortalities (45.5%), of which 3 were attributed to TEN, 1 to SJS and 1 to DRESS. Most of them succumbed due to a combination of factors like sepsis, pneumonia, and multi-organ failure.

DISCUSSION

From our 10-year review, the rate of hospital admission due to SCARs was 0.3/1000, similar to other international papers by Lee HY et al. (Singapore)[4], Grando LR et al. (Brazil)[14] and Li LF et al. (China).[15] However, this was only half the rate reported by Fiscenson-Albala F et al. (France).[16] SCARs contributed 0.42% of our new dermatology clinic attendance which was much lower than the other Malaysian cohort reported by Choon et al. (0.86%) in 2011.[17] There was also a marked decline in SCARs cases seen in our department since the year 2011 as shown in Figure 2. This improvement may be attributed to increased doctor awareness, which translated to a more judicious prescribing habit. In the year 2011, active measures were implemented by the Ministry of Health of Malaysia to curb the alarming issue of rampant allopurinol use among medical practitioners. The prescribing category for allopurinol was raised from Category B (can be prescribed by medical officers) to Category A/KK (only can be prescribed by consultants/specialists/family physician specialists). Reminders were issued to doctors who used allopurinol without justified indication. Uric acid analysis, which was once part of the routine renal function profile was also removed. This is to curb the unnecessary treatment of asymptomatic hyperuricemia without associated complications. The magnitude of adverse reactions caused by allopurinol was detected due to the collaborative efforts of all health care providers in reporting all the reactions to MADRAC. This enabled remedial actions to be implemented.

In terms of demographics, the ethnic distribution of SCARs corresponded to both the hospital and clinic patient ethnic composition (Malay 45%, Chinese 33% and Indian 17%), except that in DRESS, there were more Chinese (12 out of 24 cases). However, due to the small sample size, this was statistically insignificant (*p=0.054*). More male patients were seen in DRESS and AGEP although the overall SCARs have a female predominance. The discordance of gender discrepancy is also found in various other literature reviews. Previously, SJS/TEN affected females more frequently with

some data even showing the prevalence were high as twice than of males.[18,19] However, several studies reported equal gender involvement,[20,21] while others showed a male preponderance.[15,17,22] SCARs are more commonly seen with increasing age due to the associated co-morbidities requiring polypharmacy.

The definition of SCARs is ever evolving as we understand the disease more. This is evidenced by the recent inclusion of a new clinical entity such as GBFDE by RegiSCAR study. The diagnosis of DRESS in my study is based on RegiSCAR criteria, which was implemented later in 2009.[23] Thus, with a more standardised diagnostic criterion, more cases of DRESS were accurately recognised. In our setting, only two out of nine cases of FDE fulfilled the diagnostic criteria of GBFDE based on clinical presentation and BSA involvement. This is one of the limitations of a retrospective study where the diagnosis is made based on findings recorded. From this study, we learned that a more structured and detailed information is crucial in adverse drug reaction reporting in order to capture the true number of cases. We believed that with the inclusion of GBFDE in the RegiSCAR study, more GBFDE cases will be reported.

Allopurinol being the most common agent contributing to SCARs, is consistent with studies from Asia, Europe and Israel.[17,22,24] However, this does not hold true in the city districts of China,[15] India[25] and Jamaica[21] where antibiotics and anticonvulsants were the main culprits. This discrepancy might be due to the different prescribing practices in different countries. A nationwide population-based study in Taiwan concluded that the risk factors for allopurinol hypersensitivity included female sex, age 60 years or older, initial allopurinol dosage exceeding 100mg/d, associated renal or cardiovascular comorbidities and treatment of asymptomatic hyperuricemia.[26] Many studies have elucidated the strong genetic predisposition of allopurinol-induced SJS/TEN with HLA-B *5801, as seen in Han Chinese in Taiwan,[27] Japanese,[28] Koreans,[29] European[30] and Malaysia.[31] Somkrua et al.'s meta-analysis on allopurinol-induced SJS/TEN concluded that the risk was significantly increased by 80 to 97 times among HLA-B* 5801 patients compared to those without the gene. This association was consistent in both Asian and Non-Asian populations.[32] Moreover, we also noticed that allopurinol is responsible for most of the DRESS cases (46%), which is similar to Taiwan studies[7] and other local studies such as Ding WY et al.[33] (52.6%), Choon SE et al.[17] (44%) and Tee SH et al.[22] (40%). The role of genetic testing for HLA-B*5801 prior to allopurinol administration should be considered as it may be potentially cost-effective as well as life-saving if we were to take into consideration the high morbidity and mortality imposed by allopurinol-induced SJS/TEN. Ko TM et al.[34] supported the use of genetic screening of HLA-B*58:01 before initiating allopurinol therapy. There was a significant reduction of incidence of allopurinol-induced SCARs from seven expected cases to none in their cohort study.

Other common culprits include over-the-counter drugs such as paracetamol, cetirizine, ranitidine, omeprazole and antihypertensives (amlodipine, diltiazem and frusemide). Hence, we should always bear in mind the risk of drug adverse reactions when prescribing medications and at the same time share this knowledge and awareness not just among doctors but also other healthcare workers like pharmacists and paramedics.

In this study, 99% of the administrated drugs showed the typical interval period of two months from drug administration to the onset of the symptoms. With this crucial information, it is important to remind and educate our patients to observe the signs and symptoms of CADR especially during the first two months as prompt withdrawal of the offending medication, especially on the first appearance of skin lesions can improve the outcome tremendously. Gracia-Doval I et al.[35] concluded that the earlier the withdrawal of the causative agent, the better the prognosis with an odds ratio of 0.69 for each day (95% confidence interval, 0.53-0.89) as well as lowering the mortality rate by 30% per day. This is especially so with the shorter half-life drugs (<24 hours). One should always anticipate the possibility of SCARs and an earlier follow-up appointment (within the first two months) is crucial for patients treated with high-risk medications for the first time. The time frame between the onset of DRESS and drug administration is longer, at 29.4 days which corresponds to RegiSCAR definition of three weeks or more.

The main treatment for SCARs includes immediate withdrawal of the offending drugs with adequate supportive care. To date, the use of systemic corticosteroid in SJS/TEN remains highly controversial. This is due to the lack of prospective, randomized controlled trials in this group of patients. From our observation and experience of local experts, the use of corticosteroid in SJS may provide symptomatic relief, although the mortality rate, unfortunately, remains unchanged. From our study cohort, systemic corticosteroid (5.8%) was used based on a case-to-case basis depending on the cause, complications and patients' comorbidities. It is not a routine practice, and can only be given to patients with a progressive disease when the benefits outweigh their potential harms like sepsis, gastrointestinal bleeding, stress ulcer and poor wound healing. Contrary, several studies do not recommend the use of corticosteroid due to the increased risk of infection and thus prolonging hospitalisation.[36,37] On the other hand, some studies have shown improved outcome with reduced mortality.[6,38] A retrospective study by Yang et al. highlighted the role of combination therapy between systemic corticosteroid and intravenous immunoglobulin (IVIg) in SJS/TEN in order to shorten the hospitalisation duration and arrest the disease progression compared to systemic corticosteroid monotherapy.[39]

Intravenous immunoglobulin (IVIG) was only used in SJS (6 out of 104 cases) and TEN (33 out of 45 cases). The use of IVIG in the management of TEN is controversial. Some studies using high-dose IVIg have shown a trend towards improved mortality and children treated with IVIg had a good prognosis. A recent meta-analysis by Huang et al.[40] (2016) did not support the clinical benefits of high dose IVIg for TEN.

In order to reduce the incidence of adverse drug reactions, we do recommend a thorough history taking especially a detail drug history with an equal importance on family history of adverse drug reactions. This is because some forms of CADRs have a genetic predisposition. Secondly, genetic testing for carbamazepine and allopurinol should be considered prior to prescribing the drugs. Thirdly, a checklist system can be started for both medical practitioners and pharmacists to counter-check the medication indication to avoid

unnecessary prescription, previous drug adverse reaction and family history prior to dispensing the high risks drugs. A warning pictorial pamphlet with types of CADRs and possible lists of high-risk drugs should be given to patients to increase the awareness so that they are able to recognise earlier signs of cutaneous drug reactions and sought medical attention promptly. Last but not least, there should be equal emphasis on the importance of notification of CADRs to drug authority among healthcare workers. Therefore, the role of MADRAC to educate and share the updated drug information among healthcare workers is crucial.

CONCLUSION

The commonest manifestations of SCARs in our setting are SJS, TEN and DRESS. Allopurinol remains the most common culprit. Thus, judicious allopurinol use is advocated and pre-emptive genetic screening for HLA-B *5801 should be considered.

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