A study of severe cutaneous adverse drug reactions in Iranian patients

Hossein Mortazavi, MD [1]
Alireza Mortazavi, PhD [2]
Anahita Rostami, MD [1*]
Mohammadreza Javadi, PhD [2,3]
Robabeh Abedini, MD [1]
Amir Teimourpour, PhD Candidate [4]
Kheirolah Gholami, PhD [2,3]
Ali Khamesipour, PhD [4]

1. Department of Dermatology, Tehran University of Medical Sciences, Razi Hospital, Tehran, Iran
2. Department of Clinical Pharmacy, School of Pharmacy, Tehran University of Medical Sciences, Tehran, Iran
3. Research Center of Rational Use of Drugs, Tehran University of Medical Sciences, Tehran, Iran
4. Center for Research and Training in Skin Diseases and Leprosy, Tehran University of Medical Sciences, Tehran, Iran
**Corresponding author:*
Anahita Rostami, MD
Razi Hospital, Vahdat Eslami Square, Tehran, Iran
Email: annahitarostami@gmail.com

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Background: Little data on severe cutaneous adverse drug reactions (SCADRs) is available, especially in Iran. Therefore, there is a need for more studies in this field. We aimed to evaluate the clinical pictures and laboratory data of patients with SCADR in a tertiary dermatology center in Tehran, Iran.

Methods: In this retrospective study, patients with a clinical diagnosis of SCADR based on the World Health Organisation's definition and histopathologic findings were included. Causality and preventability measures were assessed based on previous criteria, including the Naranjo score and the Schomock and Thronton scale.

Results: Thirty-nine patients with a mean age of 43 ± 17 years participated in the study. SCADRs were more common in females than in males (2.9/1). SCADRs included Stevens-Johnson syndrome/toxic epidermal necrolysis (SJS/TEN), acute generalized exanthematous pustulosis (AGEP), and drug reactions with eosinophilia and systemic symptoms (DRESS). Thirty-one patients presented a Naranjo score of 5-8, indicating probable drug reactions. The remaining eight patients (with scores of 1-4) were determined as having possible drug eruptions. Regarding the category of culprit drugs, anticonvulsants (49%), antimalarials (15%), antibiotics (13%), and antihypertensives (10%) were the most frequent causes of SCADR, with lamotrigine being the single most common agent.

Conclusion: The most frequent clinical presentation of SCADR was SJS/TEN, followed by AGEP and DRESS. The most frequent cause of SCADR was anticonvulsant drugs.

Keywords: adverse drug reaction reporting system, anticonvulsant, antimalarial, antibiotic

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INTRODUCTION

Cutaneous adverse drug reactions (CADRs) are unwanted effects of drugs intended to treat diseases in normally prescribed doses [1]. CADRs can be classified into two groups: benign and severe [2]. According to the World Health Organization (WHO), severe cutaneous adverse drug reactions (SCADRs) are reactions that require or extend hospitalization. These reactions are life-threatening and result in significant disability. Such reactions include Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), drug-induced hypersensitivity syndrome (DIHS), and drug reactions with eosinophilia and systemic symptoms (DRESS) [3]. According to Duong *et al.*, SJS/TEN, acute generalized exanthematous pustulosis (AGEP), and DRESS are classified as SCADRs, while other

authors also regard erythroderma due to drugs as a SCADR [3,4]. Several cases of erythroderma caused by dermatologic disorders such as psoriasis and other dermatoses are indistinguishable from drug erythroderma. Therefore, erythroderma was not included in our study's definition of SCADR.

SCADRs might be fatal and induce chronic and severe sequels [3]. Investigations of CADRs are essential for evaluating their impact on healthcare in general as well as the burdens they impose on affected patients [5].

The pathogenesis of SCADRs consists of subtypes of type IV hypersensitivity reactions (Coombs and Gell classification of hypersensitivity), namely SJS/TEN as an example of type Ivc, and DRESS and AGEP as examples of type IVa and IVd hypersensitivity reactions [3,6].

To date, few *in-vitro* research works have attempted to identify drugs that cause SCADRs. High clinical suspicion, knowledge of the most frequent causative agents, the latency time between drug intake and the onset of CADR, recovery times, and awareness among at-risk groups are requirements for diagnosing and preventing SCADRs [7]. On the other hand, CADRs are not static but instead vary over time in terms of their frequency, culprit drugs, and clinical presentations [8]. Few comprehensive epidemiological studies on CADR have been reported in an Iranian context [9].

Therefore, we collected data on SCADRs including AGEP, SJS/TEN, and DIHS/DRESS in the Department of Dermatology of Tehran University of Medical Sciences (TUMS), a tertiary skincare center where the evaluations were made of the most frequent clinical types of SCADRs, culprit drugs, latency times between drug intake and the onset of CADR, and their basic demographic features.

PARTICIPANTS AND STUDY DESIGN

In a retrospective observational study conducted from February 2012 to December 2017, the files of hospitalized patients diagnosed with a SCADR in the dermatology wards of Razi Hospital of Tehran, Iran (the dermatology hospital affiliated with TUMS) were reviewed. The selection criteria of SCADR were as follows: definite diagnosis based on the WHO definition, histopathology in favor of SCADR, a sufficient interval between the first drug administration and the onset of a reaction, and improvements in the patient's condition after drug discontinuation. In addition, the included patients had a Naranjo scale score of ≥1 (≥ 9: definite ADR; 5–8: probable ADR; 1–4: possible ADR) [10].

Based on WHO's definition, SCADRs are CADRs requiring hospitalization or extending a patient's hospital stay, resulting in persistent or significant disability or life-threatening outcomes [11].

Patients who did not have histopathology in favor of drug eruption were excluded. Also, patients with cutaneous drug eruptions who did not fulfill the WHO criteria for SCADR were excluded (according to the WHO, patients with SCADR need hospitalization). Patients with erythroderma were also excluded.

Differential diagnoses were ruled out with clinical and histologic evaluations. Patients' files held by the department of medical records of the Razi Skin Hospital (affiliated to TUMS) were reviewed for the extraction of data, including demographic characteristics (age, sex), suspected drugs used, route of drug administration, the time interval between drug intake and the onset of the reaction, physical examinations (to determine the pattern of drug eruption), and sites of involvement, as well as each patient's outcomes, previous drug allergies, and medical history. Laboratory assessments were analyzed, including complete blood counts (especially eosinophil count), renal functions, liver functions, and erythrocyte sedimentation rate (ESR).

Causality and preventability were assessed using previous criteria [12]. Preventability was assessed using the modified Schomock and Thronton scale, and the CADRs detected using this scale were classified as either definitely preventable or not preventable [13].

The project was approved by the Ethics Committee, Deputy of Research, TUMS (IR.TUMS.REC.1394.106).

Statistical analysis

The independent t-test, one-way ANOVA, and chi-square test were used to analyze the data. All statistical analyses were performed in SPSS 24.

RESULTS

Thirty-nine patients were admitted with a diagnosis of SCADR. The mean age of the patients was 43 ± 17 years (range 15 to 86). The demographic data of the patients with SCADRs (gender, age, lag period, past drug history, duration of hospitalization, corticosteroid dosage, comorbidities, and smoking status) are shown in Table 1.

Clinically, all patients had a fever (> 37.8°C). Also, pruritus was observed in 31 patients, pain in 11, scaling in 11, and mucosal involvement in 21 patients (including 15 equals 78.94% in TEN/SJS, two equals 66.66% in DRESS, and four equals 23.52% in AGEP). Non-cutaneous manifestations were observed in 74.3% of the cases. Furthermore, gastrointestinal problems (nausea, vomiting, abdominal pain, dysphagia, and odynophagia) were seen in 26% of the patients. Dysuria (24%), malaise and arthralgia (19%), and coughing (3%) were the most common manifestations. Abnormal laboratory findings are shown in Table 2.

Regarding histopathologic findings, full-thickness epidermal necrosis and a negative direct immunofluorescence test (for autoimmune bullous diseases, such as pemphigus and pemphigoid) were the major criteria for TEN and SJS. Neutrophilic infiltrates of a spongiform or non-spongiform pattern and subcorneal or intra-epidermal pustules were the most frequent histological findings among AGEP cases. Compared to pustular psoriasis, larger eosinophil infiltrates, infrequent necrotic keratinocytes, larger mixed dermal infiltrates, and the absence of dilated blood vessels were more in favor of AGEP. Furthermore, the histopathological patterns of DRESS were non-specific [14]. Eczematous lesions and interface dermatitis were the most frequent patterns. All causality and preventability assessment scores are shown in Table 3.

The most common underlying diseases that

Table 1. Demographic data of the patients with SCADRs (severe cutaneous adverse drug reactions)

Demographic data	AGEP	TEN/SJS	DRESS	Total N (%)	Mean ± SD	*P*
Gender N (%)						
Female	13 (76.5)	13 (68)	3 (100)	29 (74.3)	-	
Male	4 (23.5)	6 (32)	0 (0)	10 (25.7)	-	0.431
Total	17 (43.6)	19 (48.7)	3 (7.7)	39		
Age (mean, SD)	43 ± 16	44 ± 19	36 ± 18	-	43 ± 17	0.716
Lag period (days) (mean, SD)	13 ± 10	13 ± 9	21 ± 7	-	20 ± 23	0.827
Past drug history N (%)	5 (29.4)	2 (13.3)	0	7 (18)	-	0.265
Duration of hospitalization (days) (mean, SD)	5 ± 3	7 ± 4	4 ± 2	-	6 ± 4	0.345
Corticostreoid dosage (mg/day) (mean, SD)	26.67 ± 9.01	34.38 ± 9.64	26.67 ± 15.28	-	31.07 ± 10.4	0.253
Comorbidities N (%)						
HTN	4 (23.5)	3 (15.8)	1 (33.3)	8 (20.5)	-	0.593
DM	1 (5.9)	2 (10)	0	-	-	1.00
Asthma	0	1 (5.3)	0	1 (2.6)		1.00
Smoking N (%)	2 (11.8)	3 (15)	0	5 (12.8)	-	0.728

Abbreviations: AGEP: acute generalized pustular dermatosis, TEN: toxic epidermal necrolysis, SJS: Stevens-Johnson syndrome, DRESS: drug reaction with eosinophilia and systemic symptoms, HTN: hypertension, DM: diabetes mellitus, N: number, %: percent, SD: standard deviation

Table 2. Abnormal laboratory findings in patients with SCADRs (severe cutaneous adverse drug reactions)

Variable	Normal value	AGEP (17)	TEN/SJS (19)	DRESS (3)	Total (39)
Leukocytosis	(3.54-6.06)	14 (82.35%)	14 (73.68%)	1 (33.33%)	29 (74.36%)
Lymphocytosis	(1 – 4.8)	0.0 (0.0%)	0.0 (0.0%)	1 (33.33%)	1 (2.56%)
Eosinophilia	(0 - 0.06)	4 (23.53%)	8 (42.1%)	3 (100%)	15 (35.89%)
Neutrophilia	(1.5 – 8.0)	7 (41.18%)	6 (31.58%)	1 (33.33%)	14 (38.46%)
Elevated ALT (SGPT)	(7 – 55)	1 (5.88%)	10 (52.63%)	2 (66.67%)	13 (33.33%)
Elevated AST (SGOT)	(12 – 38)	1 (5.88%)	11 (57.89%)	2 (66.67%)	14 (35.89%)
Elevated Creatinine	(0.6 – 1.2)	4 (23.53%)	1 (5.26%)	1 (33.33%)	6 (15.38%)
Elevated ESR	(0 – 20)	5 (29.41%)	7 (36.84%)	0.0 (0.0%)	12 (30.77%)

Abbreviations: WBC: wight blood cells, ALT: alanine aminotransferase, AST: aspartate aminotransferase, ALKP: alkaline transferase, IU/L: international units/liter, ESR: erythrocyte sedimentation rate, SCADR: severe cutaneous adverse drug reaction

Table 3. Causality, severity, and preventability assessment of SCADR (severe cutaneous adverse drug reaction)

Method of assessment	Assessment	AGEP N (%)	TEN/SJS N (%)	DRESS N (%)	Total N (%)
Naranjo algorithm*	Probable	13 (76)	16 (84)	2 (66)	31 (79.4)
	Possible	4 (14)	3 (6)	1 (33)	8 (20.5)
Preventability **	Definite	3 (17)	2 (10)	0.0 (0.0%)	5 (12.8)
	Not preventable	14 (82.3)	17 (89.5)	3 (100)	34 (87.2)

*Reference: 11. ** Schumock and Thornton scale
Abbreviations: AGEP: acute generalized pustular dermatosis, TEN: toxic epidermal necrolysis, SJS: Stevens-Johnson syndrome, DRESS: drug reaction with eosinophilia and systemic symptoms, N: number, SCADR: severe cutaneous adverse drug reaction

justified the use of drugs were neuropsychiatric disorders such as seizure and epilepsy (nine patients), rheumatoid arthritis (six patients), major depression (three patients), hypertension (three patients), pain-related disorders or neuralgia (three patients), brain tumor (two patients), brain trauma (one patient), cerebrovascular accident (one patient), and cellulitis (one patient), respectively. In 10 patients, the underlying diseases for using the culprit drugs were not mentioned.

The culprit drug for each disease is shown in Table 4. The distribution of the drug categories is depicted in Figure 1.

Thirty patients (76.92%) were treated with systemic corticosteroids, including oral prednisolone and intravenous/intramuscular dexamethasone (Table 1). Oral antihistamines and topical corticosteroids were also prescribed.

Follow-up

Two TEN patients with systemic involvement and critical conditions were transferred to the intensive care unit (ICU). We did not have access to the patients' information after they were transferred to ICU. The rest of the patients were cured.

Table 4. Culprit drugs (drug name and category) for each of the diseases

Disease	Culprit drugs			
	Category	Drug name	Count	Total (%)
AGEP	Anticonvulsants	Carbamazepine Lamotrigine	2 1	3 (17.65%)
	Antihypertensive	Losartan (ARB) Diltiazem (CCB)	1 2	1 (5.9%) 2 (11.76%)
	NSAID	Ibuprofen	1	1 (5.9%)
	Antibiotics	Co-trimoxazole Cephalosporin	1 1	2 (11.76%)
	Anti-malarial	Hydroxychloroquine	5	5 (29.41%)
	PPI	Omeprazole	1	1 (5.9%)
	Anti-fungal	Terbinafine	1	1 (5.9%)
	Non-specific	Others	1	1 (5.9%)
	Total	-	17	17 (100%)
TEN/SJS	Anticonvulsants	Carbamazepine Lamotrigine Phenytoin	4 7 2	13 (68.42%)
	NSAID	Diclofenac	1	1 (5.26%)
	Antihypertensive	Losartan (ARB)	1	1 (5.26%)
	Antibiotics	Cephalosporin Carbapenem Rifampin	1 1 1	3 (15.79%)
	Anti-malarial	Hydroxychloroquine	1	1 (5.26%)
	Total	-	19	19 (100%)
DRESS	Anticonvulsants	Lamotrigine Carbamazepine	2 1	3 (100%)
	Total	-	3	3 (100%)

Abbreviations: ARB: angiotensin II receptor blocker, CCB: calcium channel blocker, NSAID: nonsteroidal anti-inflammatory drug, PPI: proton-pump inhibitor

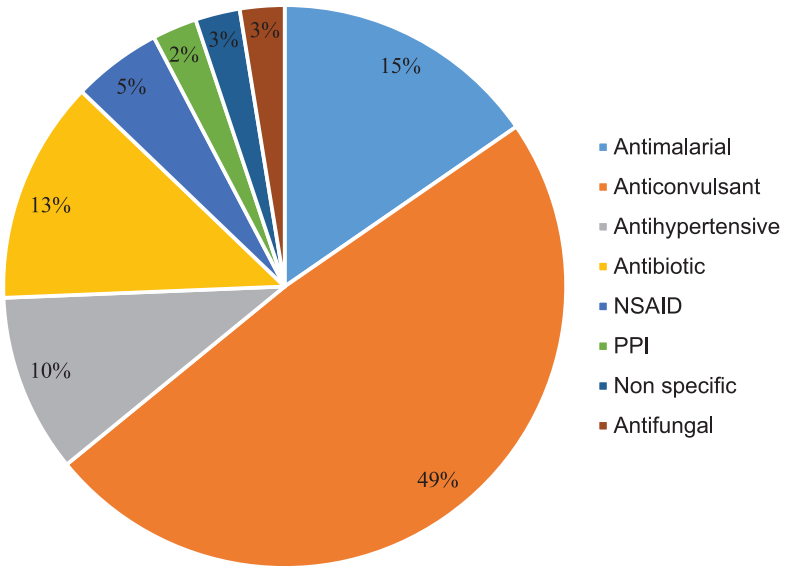

Figure 1. Percentage of the category of culprit drugs responsible for SCADR (severe cutaneous adverse drug reaction)
Abbreviations: NSAID: nonsteroidal anti-inflammatory drug, PPI: proton-pump inhibitors, SCADR: severe cutaneous adverse drug reaction

DISCUSSION

In the present study, the total number of SCADRs was higher in female patients than in male patients. Most of the patients were aged between 26 and 60 years, which corroborates previous studies. Similarly, Guzman *et al.* found that SCADRs were slightly more prevalent in women than in men, and the mean age of patients was 50 years [15]. Meanwhile, Wang *et al.* reported that the ratios of non-severe and severe CADRs were similar in men and women, with men being affected more often than women [8]. Generally speaking, adverse reactions to drugs depend on the structure and chemistry of the drug, the immune system of the host, the drug dose, the gender of the patient, and the presence of specific HLA alleles [6]. In addition, according to some authors, SCADRs – especially SJS/TEN – are more prevalent in females than in males, which is supported by our findings [4,15]. However, there are some discrepancies among existing studies.

Our results do not indicate any significant influence of comorbidities, smoking, or past drug history on the occurrence rate of CADRs. However, the findings of Padmavathi *et al.* indicated that a history of allergies is a significant risk factor for drug allergies [11]. Also, comorbidities can indirectly affect a patient's reaction to drugs – for example, patients with comorbid diseases more frequently use drugs for their medical problems [15].

Drug interactions may increase the risk of drug reactions and have effects on the epidemiology of drug reactions in older adults. Due to multiple problems and increased medical illnesses in this population, the use of benzodiazepines, neuroleptics, antihypertensives, and antibiotics is increased, so the rate of drug reactions may also increase [16].

In this retrospective observational study, TEN/SJS was the most common clinical pattern of SCADR, followed by AGEP and DRESS. In a meta-analysis performed by Deng *et al.* in 2017, SJS/TEN was the most common clinical pattern of SCADR [17]. In the present study, AGEP and DRESS were the second and third most common clinical pictures of SCADR. Meanwhile, in a study of SCADRs in children, 12% of patients had AGE*P* [18]. In other research, Deng *et al.* found that only 1.6% of patients had DRESS. On the other hand, in another work, DRESS (found in 50% of cases) was the most common clinical presentation among SCADRs [15]. Differences in the number of clinical subtypes of SCADR might be due either to the genetic predisposition of different populations or diversity of drug usage in clinical practice [3].

The range of lag periods reported in the Duong *et al.* study for AGEP (1-11 days), TEN/SJS

(4-28 days), and DRESS (2-6 weeks) was similar to data presented in our study [3] (Table 1).

As in previous studies [12,19], the causality of drug eruption was determined in the current study based on Naranjo scores. Most of the patients had a Naranjo score assigned as "possible" (Table 3), and most cases were classified as "not preventable". Only five patients showed a previous history of reactions with the same drug, which is responsible for the definitely preventable cases in our study. These five cases could be prevented by alerting the patients and reducing the economic burden of SCADRs. Similar to our findings, Padmavathi *et al.* revealed that 12.2% of CADRs were definitely preventable [12].

Mucosal involvement was seen most commonly in patients with SJS/TEN, followed by DRESS then AGEP. However, Misirlioglu *et al.* showed that mucosal involvement was reported in all patients with SJS/TEN and only 12.5% of the patients with DRESS [18]. More than half of our patients experienced mucosal involvement, whereas 63.8% of cases showed mucosal involvement in Deng *et al.*'s [17] work. In our study, more than three-fourths of the patients with TEN/SJS had oral mucosal involvement; 85.4% of the patients in Kim *et al.*'s study had oral mucosal involvement [20].

Regarding laboratory data (Table 2), the highest levels of leukocytes were seen in patients with AGEP, followed by those with SJS/TEN and DRESS. In a study by Misirlioglu *et al.*, 100% of the patients with AGEP, 56.3% of patients with DRESS, and 34.3% of patients with SJS/TEN had leukocytosis [18]. Eosinophilia was detected in all patients with DRESS syndrome at a rate similar to a previous study [18]. Additionally, elevated liver enzymes, including ALT and AST, were observed in about one-third of patients. These findings are similar to the 41.8% elevation of liver enzymes reported by Deng *et al.* [17]. Elevated levels of ESR were found more frequently in patients with SJS/TEN and AGEP (Table 2). Meanwhile, in the study by Misirlioglu *et al.*, 62.9% of patients with SJS/TEN and 56.3% of patients with AGEP exhibited elevated levels of ESR [18]. Compared with our study, more cases of elevated ESR were reported in Misirlioglu *et al.*'s study.

Regarding culprit drugs (Table 4, Figure 1), the predominance of anticonvulsant agents (as seen in our study) has been reported previously [5]. In two other studies, antibiotics were the most frequent cause of SCADRs [17,21]. According to our findings, the most common cause of SJS/TEN was anticonvulsants (lamotrigine, carbamazepine) (Table 4). In two other studies, anticonvulsants were the most common cause of SJS/TEN [22,23].

In the present study, neuropsychiatric disorders were the most common underlying disease that justified the use of drugs, which agrees with the results produced by Grando *et al.* [5]. However, in other studies, infections were reported as the most common underlying disorder [21,24]. These differences can be due to the non-registration of over-the-counter antibiotics. On the other hand, some anticonvulsants like carbamazepine may be more likely than antibiotics to cause SCADRs [8].

In the current study, the longest period of hospitalization was recorded to be 17 days for TEN/SJS patients. In general, TEN/SJS is associated with relatively long hospital stays and high costs [3]. Similar to our study, Guzman *et al.* showed that TEN/SJS was linked to the longest mean duration of hospitalization of 10 days (the overall mean duration was 6.67 days) [15].

In the present study, three-fourths of the patients were treated with systemic corticosteroids, and TEN/SJS required the highest mean dose of corticosteroids (34.38 mg prednisolone/day) for treatment, which agrees with the findings of previous studies [15,25].

In terms of study limitations, because of the absence of an equipped ICU from our center, the two end-stage patients with TEN were transferred to the ICUs of other medical centers; therefore, we do not present a mortality rate in this study. Also, there is no straightforward and reliable method for carrying out a differential diagnosis of SJS/TEN; thus, in this study, we report SJS/TEN in one category, as done so by others [3,18]. Due to the aforementioned limitations, further studies are recommended.

CONCLUSION

In this study, SJS/TEN reactions represented the most frequent clinical presentation of SCADRs. The lag periods and laboratory findings were compatible with previous reports. In order of frequency, anticonvulsants, antimalarials, antibiotics, and antihypertensives were the categories of culprit

drugs. Further studies with larger sample sizes are recommended.

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