



Cause and Treatment of Severe Cutaneous Adverse Drug Reactions at RSUP Dr. Sardjito Yogyakarta

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Abstract: SCARs is an unexpected reaction from the use of a drug which is a severe skin disorder such as SJS, TEN and DRESS. Although the incidence is low, SCAR is associated with high mortality, so needed data to show the drug that causes the biggest cause of SCAR and the treatment. The study was conducted in a retrospective descriptive with total sampling data collection techniques on the medical records of patients with a diagnosis of SJS, TEN and DRESS at RSUP Dr. Sardjito Yogyakarta from 2015 to 2019. There were 78 patients diagnosed with SCARs and 48 patients met the inclusion criteria. 23 patients diagnosed with SJS, 6 patients diagnosed with TEN and 19 patients diagnosed with DRESS. The main causative drugs in patients with SJS, TEN and DRESS were Antibiotics (50%), Analgesics (26%), Antiepileptic drugs (6%), Antidepressants, Antifungals, Antihypertensives, Antivirals was 1% for each group and other drugs (8%). The antibiotics that most often cause SCARs are Cephalosporins, Ceftriaxone and Cefixim. While the main therapy for SCARs, be it SJS, TEN or DRESS, is the use of systemic corticosteroids and supportive intravenous fluid therapy

Keywords: DRESS, SJS, TEN, Severe Cutaneous Adverse Drug Reaction (SCARs)

INTRODUCTION

Drug-Induced Disease (DID) is an unwanted effect from the use of drugs that can cause symptoms that require medical treatment (Tandon et al., 2015). Undesirable reactions from the use of drugs can be in the form of acute reactions such as anaphylactic shock, respiratory problems or severe skin disorders, as Severe Cutaneous Adverse Reactions (SCARs) (Borges et al, 2010). Severe conditions such as SCARs can be life-threatening with risk factors such as female gender, age, polypharmacy, immunosuppression and autoimmune disorders (Verma et al, 2013). SCARs consist of Stevens-Johnson Syndrome (SJS), Toxic Epidermal Necrolysis, and Drug Reaction (TEN) and Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) (Duong et al, 2017).

Despite their low incidence, SCARs are associated with high mortality with chronic autoimmune sequelae. The incidence of SCARs such as SJS and TEN is estimated at two per 1 million people, while DRESS in users of new antiepileptic drugs is estimated at one per 1000 or one per 10,000 (Wu et al., 2018).

Drugs that are often the cause of SCARs are antiepileptic drugs, antibiotics, allopurinol and non-steroidal anti-inflammatory drugs (Esmaeilzadeh et al., 2019). In the case of SJS/TEN, the drugs most often the cause are carbamazepine, phenobarbital, phenytoin and allopurinol (Velasco-Tirado et al., 2018).. In the European SCAR registry (RegiSCAR), carbamazepine is the most common cause of DRESS. Other antiepileptic drugs such as phenytoin have also been found to be associated with SCAR (Mustafa, Ostrov, & Yerly, 2018). In addition to these drugs, other drugs associated with SCAR include



antimicrobial agents (Cotrimoxazole, Vancomycin, Aminopenicillin, Minocycline, Sulfasalazine, Dapsone) and NSAIDs (Celecoxib and Ibuprofen) (Mustafa *et al.*, 2018).

The main treatment for SCARs in SJS/TEN and DRESS is stopping the causative drug. Systemic corticosteroid administration is also a specific therapy for SCARs. Rapid resolution of the rash and fever occurs several days after receiving corticosteroids. Intravenous immunoglobulin (IVIG) has been reported to be successful in patients with SCARs who do not respond to systemic steroids or are contraindicated. Supportive therapy and symptomatic therapy can be considered as treatment options in patients (Cho & Chu, 2017).

SCARs are a rare adverse drug reaction, although they can increase the mortality and morbidity rates which are quite high. There is not much literature in Indonesia that discusses SCARs, so it is necessary to conduct a study to see the profile of SCARs in Indonesian Hospitals. This study aims to determine the etiology and therapy used in SJS, TEN and DRESS patients at Dr.Sardjito Yogyakarta from 2015 to 2019.

METHODS

This study is a descriptive type of research and data collection was carried out retrospectively to see the causes of the disease and its treatment in hospitalized patients with a diagnosis of SJS/TEN and DRESS. The target population in this study were all patients diagnosed with SJS/TEN and DRESS and were hospitalized at RSUP Dr.Sardjito Yogyakarta from 2015 to 2019 who meet the inclusion criteria. Inclusion criteria were patients with known causes of SCARs, patients with primary diagnosis of SJS (L51.1), TEN (L51.2), DRESS (L27.0). The research tool used is a data retrieval form to collect clinical data from patient medical records. The data taken include patient characteristics data (medical record number, age and gender), patient clinical data (main diagnosis, comorbidities, patient therapy, and causes of SJS/TEN and DRESS). The results of the data were analyzed using descriptive analysis. Demographic features of SCARs patients include gender and age. The clinical characteristics of the patients included the causes of SCARs (SJS, TEN and DRESS) and the treatment of SCARs.

RESULT AND DISCUSSION

The number of patients diagnosed with SJS, TEN and DRESS at Dr. Sardjito Yogyakarta in 2015-2019 were 78 patients and those who met the inclusion criteria were 48 patients. Patients did not meet the inclusion criteria due to incomplete patient data. Then 23 SJS patients (48%), 6 TEN patients (13%) and 19 DRESS patients (39%) were analyzed. Patient demographic data based on age and gender will be shown in **Table 1**.

Table 1. Characteristics of SJS, TEN and DRESS

Characteristics of patients	Patients (%)			
	SJS n=23	TEN n=6	DRESS n=19	SCARs
Gender				
Male	9 (39)	4(67)	8 (42)	21 (44)
Female	14 (61)	2(33)	11 (58)	27 (56)
Age (years old)				
< 25	8 (35)	1 (17)	3 (16)	12 (25)
25-59	12 (52)	5 (83)	14 (73)	31 (65)
≥60	3 (13)	0 (0)	2 (11)	5 (10)

If seen in the **Table 1** of patient demographic characteristics based on gender and age, the incidence of SCARs was more common in women, namely 56% compared to 44% for men. In SJS patients as much as 61% experienced by women and 39% experienced by men. The highest percentage



of events in women also occurred in DRESS's patients, 58% experienced by female patients. Meanwhile, in TEN patients, the highest incidence was experienced by male patients, which was 67%.

This is in accordance with the results of a follow-up study from the National Institute of Allergy and Infection Disease that women or women have a tendency to suffer from a more severe allergic reaction than men. When viewed from the results of trials on mice, this is because the female hormone estrogen increases the activity of enzymes that cause allergic reactions (Fransisca, 2015). However, in the study of Wang and May (2017), it was stated that gender was not associated with the occurrence of mortality in SJS and TEN patients (Wang dan Mei, 2017).

There are several factors that influence the occurrence of hypersensitivity reactions such as genetic factors, exposure factors, and environmental factors. Hypersensitivity reactions will increase with the influence of exposure and the surrounding environment. Characteristics of patients based on age, namely the distribution of the most groups of patients with SJS, TEN, and DRESS in the age group of 25-59 years by 65%, followed by the age group <25 years by 25% and the age group >60 years by 10%. The causes of SCARs are shown in **Table 2**.

Table 2. Characteristics of SJS, TEN and DRESS

Causative drugs	Patient (%)			
	SJS	TEN	DRESS	SCARs
	n=35	n=8	n=22	n = 65
Antibiotic	14 (40)	6 (75)	13 (60)	33 (50)
Antiepileptic	3 (8)	0	1 (4)	4 (6)
Analgetic	9 (25)	2 (25)	6 (28)	17 (26)
Antidepressant	1 (3)	0	0	1 (1)
Antifungal	1 (3)	0	0	1 (1)
Antihypertension	1 (3)	0	0	1 (1)
Antiviral	2 (6)	0	1 (4)	3 (5)
Other drug	4 (11)	0	1 (4)	5 (8)

Based on the results from the **Table 2** above, it is known that the highest cause of the incidence of SCARs is the use of antibiotics by 50% followed by analgesics 26%, antiepileptic drugs (6%), 1% was for each antidepressants, antifungals, antihypertensives, antivirals and other drugs (8%). If seen in **Table 3** there are some patients who are caused by more than 1 drug class. The cause of the largest drug class in SJS patients is Antibiotics (40%), Analgesics (25%), Antiepileptic (8%), Antivirals (6%), Antifungal and Antihypertensive, Antidepressants each 3% and other drugs (11%). In TEN patients, Antibiotics (75%) and Analgesics (25%) were used, and in DRESS patients, the largest group was Antibiotics (60%), Analgesics (28%), 4% for each Antiepileptic, Antiviral and other drugs.

The class of antibiotics that cause the most of the cephalosporins such as ceftriaxone, cefixime and ceftazidime, antibiotics of the antituberculosis group, and ciprofloxacin. The analgesic group that caused the highest incidence was diclofenac sodium, paracetamol, ibuprofen and mefenamic acid. Other drugs such as allupurinol, dexamethasone, gemfibrozil and antiepileptic drugs such as phenytoin, carbamazepine and valproic acid. These results are in accordance with research which shows that the class of antibiotic drugs is the cause of the most common cases of SCARs occurring terjadi (Wang & Mei, 2017a)(Anna R. *et al*, 2019)(S.H. Kardaunet *al*, 2007). .The Data showed therapy in SJS, TEN and DRESS patients will be shown in **Table 3**.



Table 3. Therapy on the Incidence of SCARs at RSUP Dr. Sardjito Yogyakarta 2015-2019

Therapy	Patient (%)			
	SJS n=23	TEN n=6	DRESS n=19	SCARs N=48
Sistemic				
Corticosteroid	23 (100)	6 (100)	19 (100)	48(100)
Antibiotics	10 (43)	5 (83)	1 (5)	16(33)
Antihistamin	12 (52)	3 (50)	8 (42)	23(48)
Imunoglobulin	1 (4)	0	0	1(2)
Antikoagulan	4 (17)	0	0	4(8)
Topical				
Moisturizer	3 (13)	0	6 (32)	9(19)
Corticosteroid	7 (30)	0	2 (11)	9(19)
Antibiotic	30 (130)	1 (17)	2 (11)	33(69)
Antifungal	6 (26)	0	1 (5)	7(15)
Supportive				
Intravenous fluids	23 (100)	6 (100)	19 (100)	48(100)
Simpptomatics				
Analgetics	8 (35)	2 (33)	0	10(21)
Antipyretic	7(30)	2 (33)	1 (5)	10(21)

Based on **Table 3**, all patients who experienced SCARs received systemic corticosteroid therapy (100%) and supportive intravenous fluid therapy (100%). SCARs patients receiving systemic antibiotics (33%), antihistamines (48%), immunoglobulins (2%) and anticoagulants (8%). Topical therapy in DRESS patients was mostly with the use of topical antibiotics (69%), topical corticosteroids (19%), topical antifungals (15%) and moisturizers (19%). As many as 21% of DRESS patients received symptomatic therapy in the form of analgesics and antipyretics.

Systemic corticosteroids are the mainstay of treatment for patients with SCARs. Time to repair the rash on the skin quickly occurs a few days after receiving corticosteroids (Cho & Chu, 2017). Supportive therapy that is not added to other therapies may be considered as the treatment of choice in patients with SCARs. One study reported that patients who received hydration therapy recovered completely within 7 - 37 days after discontinuation of the suspected drug (Uhara *et al.*, 2013). Other studies have also shown that in cases that were only treated with supportive therapy, almost all recovered well (Ushigome *et al.*, 2013). Intravenous immunoglobulin (IVIG) therapy has been reported to be successful in patients with DRESS conditions who previously did not respond to systemic corticosteroids (Cho & Chu, 2017).

CONCLUSION

The main causes of patients with SJS, TEN and DRESS are antibiotics and analgesics. The Antibiotics that most commonly cause SCARs are Cephalosporins, Ceftriaxone and Cefixim. While the main therapy for SCARs, be it SJS, TEN or DRESS, is the use of systemic corticosteroids and supportive intravenous fluid therapy.

CONFLIC OF INTEREST

The authors state that the research was conducted without any commercial or financial relationship that could be construed as a potential conflict of interest.



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