Original Article

A Nationwide Study of Severe Cutaneous Adverse Reactions Based on the Multicenter Registry in Korea

Dong Yoon Kang, MD, PhD[a], James Yun, MBBS, PhD[b,c], Suh-Young Lee, MD[d], Young-Il Koh, MD, PhD[e], Da Woon Sim, MD, PhD[e], Sujeong Kim, MD[f], Young Hee Nam, MD, PhD[g], Jung-Won Park, MD, PhD[h], Sae Hoon Kim, MD, PhD[i], Young-Min Ye, MD, PhD[j], Hye-Kyung Park, MD, PhD[k], Min-Hye Kim, MD, PhD[l], Young-Koo Jee, MD, PhD[m], Jae-Woo Jung, MD, PhD[n], Min-Suk Yang, MD, PhD[o], Sang-Heon Kim, MD, PhD[p], Jun Kyu Lee, MD, PhD[q], Cheol-Woo Kim, MD, PhD[r], Gyu Young Hur, MD, PhD[s], Mi-Yeong Kim, MD[t], Seoung Ju Park, MD, PhD[u], Yong Eun Kwon, MD, PhD[v], Jeong-Hee Choi, MD, PhD[w], Joo-Hee Kim, MD, PhD[x], Sang Hyon Kim, MD, PhD[y], Hyen O. La, MS, PhD[z], Min-Gyu Kang, MD[aa], Chan Sun Park, MD, PhD[bb], Sang Min Lee, MD, PhD[cc], Yi Yeong Jeong, MD, PhD[dd], Hee-Kyoo Kim, MD, PhD[ee], Hyun Jung Jin, MD[ff], Jae-Won Jeong, MD, PhD[gg], Jaechun Lee, MD, PhD[hh], Yong Won Lee, MD, PhD[ii], Seung Eun Lee, MD[jj], Myoung Shin Kim, MD, PhD[kk], and Hye-Ryun Kang, MD, PhD[a,d] Korean Severe Cutaneous Adverse Reactions Consortium *Seoul, Gwangju, Daegu, Busan, Seongnam, Suwon, Cheonan, Goyang, Incheon, Jeonju, Hwaseong, Anyang, Cheongju, Jinju, Jeju, and Yangsan, Korea; and Sydney, NSW, Australia*

What is already known about this topic? Drugs such as allopurinol and aromatic antiepileptics are the most frequent causative agents of severe cutaneous adverse reactions (SCARs).

What does this article add to our knowledge? Some culprit drugs show a strong preference for a specific SCAR phenotype; carbonic anhydrase inhibitors, nonsteroidal anti-inflammatory drugs, and acetaminophen preferentially cause SJS/TEN, whereas dapsone, antituberculous agents, and glycopeptide antibacterial agents are more likely to cause DRESS. A total of 6.6% of SCAR cases resulted in death, mostly within 2 months.

How does this study impact current management guidelines? Recognizing that certain drugs preferentially cause a specific SCAR phenotype can provide additional clues for identifying the culprit agent.

BACKGROUND: Because severe cutaneous adverse reactions (SCARs), such as Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), and drug reaction with eosinophilia and systemic symptoms (DRESS) rarely occur, clinical data based on large-scale studies are still lacking.

[a]Drug Safety Monitoring Center, Seoul National University Hospital, Seoul, Korea
[b]Department of Immunology and Rheumatology, Nepean Hospital, Sydney, NSW, Australia
[c]Faculty of Medicine and Health, The University of Sydney, Sydney, NSW, Australia
[d]Department of Internal Medicine, Seoul National University College of Medicine, Seoul, Korea
[e]Department of Internal Medicine, Chonnam National University Medical School, Gwangju, Korea
[f]Department of Internal Medicine, School of Medicine, Kyungpook National University, Daegu, Korea
[g]Department of Internal Medicine, College of Medicine, Dong-A University, Busan, Korea
[h]Department of Internal Medicine, Yonsei University College of Medicine, Seoul, Korea
[i]Department of Internal Medicine, Seoul National University Bundang Hospital, Seongnam, Korea
[j]Department of Internal Medicine, Ajou University School of Medicine, Suwon, Korea
[k]Department of Internal Medicine, Pusan National University College of Medicine, Busan, Korea
[l]Department of Internal Medicine, College of Medicine, Ewha Womans University, Seoul, Korea
[m]Department of Internal Medicine, Dankook University College of Medicine, Cheonan, Korea
[n]Department of Internal Medicine, Chung-Ang University College of Medicine, Seoul, Korea
[o]Department of Internal Medicine, SMG-SNU Boramae Medical Center, Seoul, Korea
[p]Department of Internal Medicine, Hanyang University College of Medicine, Seoul, Korea
[q]Department of Internal Medicine, Dongguk University Ilsan Hospital, Goyang, Korea
[r]Department of Internal Medicine, Inha University School of Medicine, Incheon, Korea
[s]Department of Internal Medicine, Korea University College of Medicine, Seoul, Korea
[t]Department of Internal Medicine, Inje University Busan Paik Hospital, Busan, Korea
[u]Department of Internal Medicine, Chonbuk National University Medical School, Jeonju, Korea
[v]Department of Internal Medicine, Chosun University Hospital, Gwangju, Korea
[w]Department of Internal Medicine, Hallym University Dongtan Sacred Heart Hospital, Hwaseong, Korea

Abbreviations used
DRESS- Drug reaction with eosinophilia and systemic symptoms
HLA- Human leukocyte antigen
ICU- Intensive care unit
IVIG- Intravenous immunoglobulin
KIDS- Korea Institute of Drug Safety and Risk Management
NSAID- Nonsteroidal anti-inflammatory drug
SCAR- Severe cutaneous adverse reaction
SJS- Stevens-Johnson syndrome
TEN- Toxic epidermal necrolysis

OBJECTIVE: To provide information on culprit drugs and clinical characteristics, including morbidity and mortality of SCARs based on a nationwide registry.
METHODS: SCAR cases that occurred from 2010 to 2015 were recruited to the Korean SCAR registry from 34 tertiary referral hospitals. Demographics, causative drugs, causality, and clinical outcomes were collected by reviewing the medical record.
RESULTS: A total of 745 SCAR cases (384 SJS/TEN cases and 361 DRESS cases) due to 149 drugs were registered. The main causative drugs were allopurinol (14.0%), carbamazepine (9.5%), vancomycin (4.7%), and antituberculous agents (6.3%). A strong preference for SJS/TEN was observed in carbonic anhydrase inhibitors (100%), nonsteroidal anti-inflammatory drugs (84%), and acetaminophen (83%), whereas dapsone (100%), antituberculous agents (81%), and glycopeptide antibacterials (78%) were more likely to cause DRESS. The mortality rate was 6.6% (SJS/TEN 8.9% and DRESS 4.2%). The median time to death was 19 days and 29 days in SJS/TEN and DRESS respectively, and 89.8% of deaths occurred within 60 days after the onset of the skin symptoms.
CONCLUSION: Allopurinol, carbamazepine, vancomycin, and antituberculous agents were the leading causes of SCARs in Korea. Some drugs preferentially caused a specific phenotype. The mortality rate of SCARs was 6.6%, and most of the deaths occurred within 2 months. © 2020 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2020;■:■-■)

Key words: *Drug-related side effects and adverse reactions; Stevens-Johnson syndrome; Drug hypersensitivity syndrome; Registries; Republic of Korea*

Severe cutaneous adverse reaction (SCAR) is a life-threatening, delayed hypersensitivity reaction. It includes Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), and drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome.[1] The incidence of SJS and TEN in the European population is estimated to be 1 to 6 and 0.4 to 1.2 per million people per year, respectively.[2,3] In Korea, the reported incidence of SJS and TEN was 3.96 to 5.03 and 0.94 to 1.45 per million people per year, respectively.[4] Previous studies estimated the occurrence of DRESS at 1 in 1000 to 10,000 exposures, but it can vary depending on the causative drugs.[2,5]

SCARs can lead to death or long-term sequelae, and the delay in discontinuing the culprit drug leads to unfavorable clinical consequences.[1-3] In patients with SJS and TEN, the mortality rate is 10% and 30%, respectively.[2-4] In DRESS cases, the mortality rate is known to be 10%, and the clinical course of DRESS appears to be more chronic.[2,3,5] In addition, SCAR results in considerable medical and social costs.[6]

Although the clinical impact on the affected individuals is enormous, epidemiologic and clinical information is limited due to its rarity and the lack of large-scale studies.[2,7] Because SCARs are often influenced by inter-racial genetic differences between countries,[8-10] data from various ethnic backgrounds should be assessed separately. The aim of this study was to investigate the current epidemiology and clinical characteristics of SCARs based on a nationwide registry in Korea.

METHODS

A nationwide registry by the Korean SCAR consortium was first established in 2014, in collaboration with the Korea Institute of Drug Safety and Risk Management (KIDS) and Drug Allergy Workgroup of the Korean Academy of Asthma, Allergy, and Clinical Immunology. Thirty-four tertiary referral hospitals participated, covering the whole country. This study was approved by the institutional review board of the ethics committees of KIDS and each participating hospital.

SCAR cases that occurred between 2010 and 2015 were identified by searching for keywords (SJS, TEN, DRESS, drug hypersensitivity, and drug eruption) in the database of individual safety case reports of adverse drug reactions, medical records of diagnoses,

[x]Department of Internal Medicine, Hallym University Sacred Heart Hospital, Anyang, Korea
[y]Department of Internal Medicine, Keimyung University Dongsan Medical Center, Daegu, Korea
[z]Department of Pharmacology, Catholic University of Korea, College of Medicine, Seoul, Korea
[aa]Department of Internal Medicine, Chungbuk National University Hospital, Cheongju, Korea
[bb]Department of Internal Medicine, Inje University Haeundae Paik Hospital, Busan, Korea
[cc]Department of Internal Medicine, Gachon University Gil Medical Center, Incheon, Korea
[dd]Department of Internal Medicine, Gyeongsang National University School of Medicine, Jinju, Korea
[ee]Department of Internal Medicine, Kosin University College of Medicine, Busan, Korea
[ff]Department of Internal Medicine, Medical school of Yeungnam University, Daegu, Korea
[gg]Department of Internal Medicine, Inje University Ilsan Paik Hospital, Goyang, Korea
[hh]Department of Internal Medicine, Jeju National University Hospital, Jeju, Korea
[ii]Department of Internal Medicine, Catholic Kwandong University College of Medicine, Incheon, Korea
[jj]Department of Internal Medicine, Pusan National University Yangsan Hospital, Yangsan, Korea
[kk]Department of Dermatology, Sanggye Paik Hospital, Inje University College of Medicine, Seoul, Korea

This study was supported by a grant from the Korean Academy of Asthma, Allergy, and Clinical Immunology and a grant from the Ministry of Food and Drug Safety of Korea (20182 MFDS445), and a grant from the Ministry of Food and Drug Safety to the Regional Pharmacovigilance Center in 2018.
Conflicts of interest: The authors declare that they have no relevant conflicts of interest.
Received for publication March 4, 2020; revised September 6, 2020; accepted for publication September 8, 2020.
Available online ■■
Corresponding author: Hye-Ryun Kang, MD, PhD, Department of Internal Medicine, Seoul National University Hospital, 101 Daehak-ro, Jongno-gu, Seoul 03080, Korea. E-mail: helenmed@snu.ac.kr.
2213-2198

https://doi.org/10.1016/j.jaip.2020.09.011

and allergy and dermatology consultation records of individuals. Once identified, a thorough retrospective review of the records was performed. Clinical data, including demographics, hospitalization, vital signs, laboratory results, clinical course, disease history, and medication history, were entered into a standardized clinical record form after reviewing the medical records. All included cases met the inclusion criteria of the RegiSCAR group.[11,12] Cases were finally registered if an allergy specialist and a pharmacovigilance physician agreed on the diagnosis of SCAR. Acute generalized exanthematous pustulosis cases were not included in this registry.

The causality of suspected drugs was assessed by the World Health Organization-Uppsala Monitoring Centre causality categories,[13] and each drug was included as a potential culprit in the analysis when the causality was assessed to be higher than "possible."

Statistical analysis was performed with SPSS version 25.0 (IBM Corporation, Armonk, NY). The *t*-test and multivariate analysis of variance were used to analyze continuous variables, and the χ^2 test was used for categorical variables.

RESULTS

Demographics of the study subjects

A total of 745 cases were finally included in the analysis after excluding invalid cases not satisfying the RegiSCAR criteria or duplicate cases due to transfers between hospitals; there were 384 patients (51.5%) with SJS/TEN and 361 patients (48.5%) with DRESS (Table I). The median age of the patients with SCAR was 56 years (interquartile range: 35-70 years), and the proportion of males was 49.0% (Table I). The most common age of onset was fifties in male (n = 87, 23.8%) and seventies in female (n = 71, 18.7%) (Figure E1, available in this article's Online Repository at www.jaci-inpractice.org). Although there was no significant difference in the age of onset according to the phenotypes (Table I), the proportion of patients under 20 years of age was significantly lower in DRESS compared with that in SJS/TEN (2.2% vs 11.5%, $P < .001$) (Figure E1, available in this article's Online Repository at www.jaci-inpractice.org).

Causative drugs of SCAR cases in Korea

A total of 149 different drugs were assessed as the cause in 745 SCAR cases. The most common culprit drugs were allopurinol (n = 104, 14.0%), carbamazepine (n = 71, 9.5%), and vancomycin (n = 35, 4.7%) (Table II; Table E1, available in this article's Online Repository at www.jaci-inpractice.org). The standard first-line antituberculous agents (isoniazid, ethambutol, rifampicin, and pyrazinamide) were also a common cause (n = 47, 6.3%) when analyzed as a group. According to the pharmacological groups, allopurinol, cephalosporin antibacterials, carboxamide containing antiepileptics (carbamazepine and oxcarbazepine), nonsteroidal anti-inflammatory drugs (NSAIDs), antituberculous agents, penicillins, other antiepileptics (classified as N03AX by Anatomical Therapeutic Chemical classification system), glycopeptide antibacterials (vancomycin and teicoplanin), quinolones, and acetaminophen were found to be the 10 major groups (Table III).

Although most of the culprit drugs caused both SJS/TEN and DRESS, there was a characteristic predilection to a specific phenotype (Figure 1). All carbonic anhydrase inhibitor—related (acetazolamide and methazolamide) cases, 84% of NSAID-related cases, and 83% of acetaminophen-related cases were SJS/TEN. On the contrary, all dapsone-related cases, 81% of antituberculous agent—related cases, and 78% of glycopeptide antibacterial—related cases of SCARs were DRESS.

Clinical characteristics and management of SCAR

The median time interval between the first intake of the culprit drug to the onset of initial symptoms was significantly longer in DRESS than in SJS/TEN (24 vs 13 days, $P = .001$), but there was no difference within SJS/TEN (Table I). The median disease duration of all patients with SCAR was 20 days, and there was no difference between SJS/TEN and DRESS. However, there was a significant increase in the disease duration within SJS/TEN, in the order of SJS, overlap, and TEN ($P < .001$) (Table I).

In terms of the route of admission, 51.2% and 33.2% of patients with SCAR were hospitalized through the emergency department and outpatient clinic, respectively. The remaining

TABLE I. Demographic and clinical characteristics of patients with SCAR

	Total	DRESS	SJS/TEN	SJS	Overlap	TEN
No. of cases (%)	745	361 (48.5)	384 (51.5)	267 (35.8)	35 (4.7)	82 (11.0)
Male (%)	49.0	50.1	47.9	46.8	45.7	52.4
Age (y), median (IQR)	56 (35-70)	55 (42-68)	56 (35-70)	54 (33-70)	61 (42-72)	56 (39-70)
Time interval from first drug intake to symptoms (d), median (IQR)*	18 (11-32)	24 (14-35)	13 (8-24)	12 (8-24)	13 (8-25)	12 (8-23)
Duration of disease from initial symptoms (d), median (IQR)†	20 (14-30)	21 (15-31)	20 (14-30)	18 (13-24)	24 (16-41)	34 (21-48)
Route of admission						
Emergency room (%)	51.2	48.6	53.6	52.7	57.1	53.7
Outpatient clinic (%)	33.2	28.1	38.1	39.4	34.3	36.5
Inpatients at the onset (%)*	15.6	23.3	8.3	7.9	8.6	9.8
Courses after admission						
ICU care (%)*,†	6.8	4.7	8.9	4.1	14.3	22.0
Recovered (%)*,†	85.2	92.8	78.1	86.1	71.4	54.9
Sequelae (%)*,†	8.2	3.0	13.0	9.4	11.4	25.6
Death (%)*,†	6.6	4.2	8.9	4.5	17.1	19.5

DRESS, Drug reaction with eosinophilia and systemic symptoms; *ICU*, intensive care unit; *IQR*, interquartile range; *SCAR*, severe cutaneous adverse reaction; *SJS*, Stevens-Johnson syndrome; *TEN*, toxic epidermal necrolysis.

*Statistically significant differences between DRESS and SJS/TEN.

†Statistically significant differences between SJS, overlap, and TEN.

TABLE II. Causative drugs of SCARs in Korea reporting at least 5 cases

	Causative drug	Total N (%)	SJS/TEN N (%)	DRESS N (%)
1	Allopurinol	104 (14.0)	51 (13.3)	53 (14.7)
2	Carbamazepine	71 (9.5)	28 (7.3)	43 (11.9)
3	Vancomycin	35 (4.7)	8 (2.1)	27 (7.5)
4	Lamotrigine	25 (3.4)	15 (3.9)	10 (2.8)
5	Acetaminophen	24 (3.2)	20 (5.2)	4 (1.1)
5	Amoxicillin	24 (3.2)	19 (4.9)	5 (1.4)
7	Ceftriaxone	22 (3.0)	9 (2.3)	13 (3.6)
7	Isoniazid	22 (3.0)	6 (1.6)	16 (4.4)
9	Cefaclor	16 (2.1)	13 (3.4)	3 (0.8)
10	Dapsone	15 (2.0)	0 (0.0)	15 (4.2)
10	Valproic Acid	15 (2.0)	5 (1.3)	10 (2.8)
12	Ciprofloxacin	14 (1.9)	7 (1.8)	7 (1.9)
13	Phenytoin	13 (1.7)	7 (1.8)	6 (1.7)
14	Ibuprofen	12 (1.6)	12 (3.1)	0 (0.0)
14	Piperacillin/tazobactam	12 (1.6)	5 (1.3)	7 (1.9)
14	Rifampicin	12 (1.6)	3 (0.8)	9 (2.5)
17	Loxoprofen	11 (1.5)	8 (2.1)	3 (0.8)
18	Sulfamethoxazole/ trimethoprim	10 (1.3)	7 (1.8)	3 (0.8)
19	Levofloxacin	9 (1.2)	5 (1.3)	4 (1.1)
19	Methazolamide	9 (1.2)	9 (2.3)	0 (0.0)
21	Aceclofenac	8 (1.1)	6 (1.6)	2 (0.6)
21	Levetiracetam	8 (1.1)	1 (0.3)	7 (1.9)
23	Cefotaxime	7 (0.9)	1 (0.3)	6 (1.7)
23	Ethambutol	7 (0.9)	0 (0.0)	7 (1.9)
23	Sulfasalazine	7 (0.9)	3 (0.8)	4 (1.1)
26	Gabapentin	6 (0.8)	3 (0.8)	3 (0.8)
26	Nafcillin	6 (0.8)	1 (0.3)	5 (1.4)
26	Pyrazinamide	6 (0.8)	0 (0.0)	6 (1.7)
29	Celecoxib	5 (0.7)	1 (0.3)	4 (1.1)
30	Dexibuprofen	5 (0.7)	5 (1.3)	0 (0.0)
30	Mefenamic acid	5 (0.7)	5 (1.3)	0 (0.0)
30	Meropenem	5 (0.7)	1 (0.3)	4 (1.1)
	Others	195 (26.2)	120 (31.3)	75 (20.8)
	Total	745 (100.0)	384 (100.0)	361 (100.0)

DRESS, Drug reaction with eosinophilia and systemic symptoms; *SCAR*, severe cutaneous adverse reaction; *SJS*, Stevens-Johnson syndrome; *TEN*, toxic epidermal necrolysis.

15.6% developed SCARs during hospitalization. The frequency of cases that occurred during the hospitalization was significantly higher in patients with DRESS compared with patients with SJS/TEN (23.3% vs 8.3%, $P < .001$) (Table I).

During the treatment of SCARs, 6.8% of patients were transferred to intensive care unit (ICU): 8.9% (n = 34) of patients with SJS/TEN and 4.7% (n = 17) of patients with DRESS ($P = .029$). Steroids were used in 92.4% of patients with SJS/TEN and 74.4% of patients with DRESS. Intravenous immunoglobulin (IVIG) therapy was used in 24.7% of patients with SJS/TEN (14.8%, 32.5%, and 51.2% in SJS, overlap, and TEN, respectively), whereas only 6.9% of patients with DRESS were treated with IVIG ($P < .001$). Other immunosuppressants such as cyclosporine were also used more frequently in patients with SJS/TEN compared with those with DRESS (5.6% vs 2.1%, $P = .017$).

Morbidity and mortality

Overall, 8.2% of patients with SCAR had long-term sequelae. Although 92.8% recovered and 3.0% had sequelae in DRESS, the prognosis in patients with SJS/TEN was relatively grave as 78.1% recovered and 13.0% had sequelae (Table I). Sequelae increased with the progression from SJS to TEN (9.4% to 25.6%, $P < .001$). Permanent damage of the skin and skin appendages was most common (73.8%), followed by ocular sequelae (36.1%) and other organs (19.6%). Among the drug groups with more than 10 cases, SCAR cases due to carbonic anhydrase inhibitors and acetaminophen resulted in the highest sequelae rates (27% and 21%, respectively) and occurred in younger age (49.4 and 37.7 years, respectively) (Table III). Among cases with sequelae, the common culprit drugs were allopurinol (n = 7), carbamazepine (n = 6), acetaminophen (n = 5), amoxicillin (n = 4), and ibuprofen (n = 3). A total of 56 drugs were suspected in 61 cases of long-term sequelae, where 27 patients (44.3%) had more than 1 suspected culprit drug (Table E2, available in this article's Online Repository at www.jaci-inpractice.org).

Overall, 6.6% of patients died from SCARs: 8.9% of SJS/TEN and 4.2% of DRESS (Table I). The mortality rates were significantly increased with progression from SJS to TEN ($P < .001$). Among the drug groups with more than 10 cases, valproic acid and quinolones-related (ciprofloxacin, levofloxacin) patients with SCAR had the highest mortality rates (20% and 17%, respectively) with relatively older age of onset (63.0 and 58.0 years, respectively) (Table III). The most common culprit drugs resulting in death was allopurinol (n = 11), followed by vancomycin (n = 4), isoniazid (n = 3), and valproic acid (n = 3). A total of 47 drugs were suspected in 49 deceased cases, where 22 patients (44.9%) had more than 1 suspected culprit drug (Table E3, available in this article's Online Repository at www.jaci-inpractice.org).

The mortality rates in patients who received IVIG therapy were 17.9% in SJS/TEN and 19.2% in DRESS, which were much higher than those without IVIG (5.7% and 2.7%, both $P < .001$). Among the patients who were transferred to the ICU, 41.2% (14 of 34 cases with SJS/TEN and 7 of 17 cases with DRESS) eventually died. If SCAR developed at the ICU, the mortality rate was as remarkably high as 75% (3 of 4 cases) in SJS/TEN and 66.7% (2 of 3 cases) in DRESS.

According to the time course, the first death occurred on the 5th day and 11th days after the initial skin symptoms in cases with SJS/TEN and DRESS, respectively (Figure 2). Half of the death cases occurred within 19 days in SJS/TEN and 29 days in DRESS. Among total patients with SCAR, 89.8% (91.2% of SJS/TEN, 86.7% of DRESS) of deaths occurred within 60 days, and the direct mortality from SCARs was reduced to 0.7% afterward. The mean age of deceased cases was 62.6 ± 17.2 years, which is significantly more than 52.6 ± 20.6 years in fully recovered cases ($P = .001$) and 50.9 ± 20.8 years in sequelae cases ($P = .002$).

DISCUSSION

This study is the most extensive and the first nationwide SCAR registry study in Korea and is one of the largest SCAR studies in the world, collecting 745 cases due to 149 different culprit drugs from 34 tertiary referral hospitals across the country. We found that the Korean patients with SCAR are older

TABLE III. Prognosis of SCARs according to the causative pharmacological groups (N ≥ 10)

	Total	SJS/TEN	DRESS	Sequelae (%)	Mortality (%)	Onset age (y)*	Hospital (d)*
Allopurinol	104	51	53	7	11	61.1	19.8
Cephalosporins	81	39	42	4	6	54.1	24.1
Carboxamide antiepileptics	73	29	44	8	1	52.6	15.2
NSAIDs	64	54	10	13	3	50.8	17.2
Antituberculous agents	48	9	39	4	8	56.2	23.7
Penicillins	48	28	20	10	4	46.6	23.0
Other antiepileptics	41	21	20	10	2	46.2	19.5
Glycopeptide antibacterials	36	8	28	6	11	63.1	26.3
Quinolones	30	16	14	13	17	63.0	24.7
Acetaminophen	24	20	4	21	0	37.7	19.5
Antineoplastic agents	15	9	6	0	13	51.9	14.9
Dapsone	15	0	15	13	0	37.8	18.9
Valproic acid	15	5	10	7	20	58.0	27.7
Hydantoin antiepileptics	14	8	6	7	0	61.6	18.3
Carbonic anhydrase inhibitors	11	11	0	27	9	49.4	25.8
Sulfonamide antibacterial	10	7	3	10	10	38.1	12.5

Carboxamide antiepileptics, carbamazepine and oxcarbazepine; Other antiepileptics, classified as N03AX by Anatomical Therapeutic Chemical classification system; Glycopeptide antibacterials, vancomycin and teicoplanin; Hydantoin antiepileptics, phenytoin and fosphenytoin; Carbonic anhydrase inhibitors, acetazolamide and methazolamide; Sulfonamide antibacterial, sulfamethoxazole/trimethoprim.

DRESS, Drug reaction with eosinophilia and systemic symptoms; *NSAID*, nonsteroidal anti-inflammatory drug; *SCAR*, severe cutaneous adverse reaction; *SJS*, Stevens-Johnson syndrome; *TEN*, toxic epidermal necrolysis.

*Mean value.

than those in the RegiSCAR cohorts (median age of onset 56 vs 50 years in SJS/TEN and 55 vs 48 years in DRESS, respectively).[14,15] Our study did not show any gender differences between the phenotypes evaluated; it was greater in SJS/TEN (male/female ratio = 0.62) compared with DRESS (male/female ratio = 0.80) in the RegiSCAR study.[15]

In our study, 149 different drugs were registered as the cause of SCARs in Korea. Allopurinol and carbamazepine were the 2 leading causes of both SJS/TEN and DRESS in our study and most other studies despite differences in ethnic susceptibility and frequency of drug usage in each country. For SJS/TEN, allopurinol was the most commonly identified causative drug in the EuroSCAR registry[14,16] and other independent studies from Italy,[17] Portugal,[18] Canada,[19] and Japan.[20] It was also the second most common causative drug of SJS/TEN in a study from Spain[21] and in the Asian registry, which includes Taiwan, Thailand, Japan, Malaysia, Singapore, Hong Kong, the Philippines, and China.[22] In the Asian registry, carbamazepine was the most common causative drug of SJS/TEN, followed by allopurinol.[22] For DRESS, allopurinol and carbamazepine were also the most common causative drugs in Korea[23] and the RegiSCAR study.[15] In terms of genetic susceptibility, allopurinol and carbamazepine hypersensitivity have been known to be associated with the presence of the human leukocyte antigen (HLA)-B*58:01 and -A*31:01, which are relatively common in Korea (12.2% and 10.3%, respectively).[24-27]

In addition to allopurinol and carbamazepine, sulfamethoxazole/trimethoprim, lamotrigine, phenytoin, phenobarbital, nevirapine, cephalosporin, and oxicam-type NSAIDs were reported to be major causes of SCARs.[5,14,15,22,28-30] However, in contrast to other studies,[21,30-32] we only found a small number of SCAR cases caused by sulfamethoxazole/trimethoprim (1.3%) and phenytoin (1.7%). Although European studies listed SCAR cases caused by oxicam NSAIDs and nevirapine to be 2.9% and 5.5%, respectively,[3,14] we found that oxicam NSAIDs accounted for only 0.4% of SCAR cases, and there was no case related to nevirapine in Korea. Vancomycin and antituberculous agents were the third and the fourth most common culprit agents in this study, respectively. Some of these regional differences in the culprit drugs can be explained by ethnic differences in the HLA allele frequency. SCARs due to carbonic anhydrase inhibitors have not been reported in ethnic groups besides the Japanese, Chinese, and Korean groups, and this seems to be related to the relatively high frequency of HLA-B*59:01 in the inhabitants of these 3 countries.[24,33,34] A high number of SCAR cases from antituberculous agents in Koreans may be related to the prevalence of HLA-C*04:01 (6.6%), which is known to increase the risk of antituberculous agent−induced DRESS.[24,35] On the contrary, HLA-A*57:01 is found in only 0.4% of Koreans and abacavir-induced hypersensitivity syndrome has not been reported in Korea until now.[24] Vancomycin was one of the major culprit drugs in Korea even though HLA-A*32:01, the genetic risk marker of vancomycin-induced DRESS, is rare (0.3%) in Koreans.[24,36] Other genetic risk factors may play a role in the development of DRESS in vancomycin users among Koreans.

Some causative drugs could not be specified when the culprit drug itself was a mixture of several drugs, or its medication information was not available (n = 13) (Table E1, available in this article's Online Repository at www.jaci-inpractice.org). In addition to general medicines, health supplements and traditional Chinese medicine were suspected as the cause of SCARs. Most of the culprit drugs were previously known to cause SCARs.

Many of the culprit drugs caused both SJS/TEN and DRESS.[2,3] However, there are some differences in culprit drugs according to the phenotypes. For example, in the previous studies, dapsone caused only DRESS,[15,32,37] whereas carbonic anhydrase inhibitors caused only SJS/TEN.[34,38] In this study, predilection to a specific phenotype in certain drugs was identified because cases of SJS/TEN and DRESS were analyzed

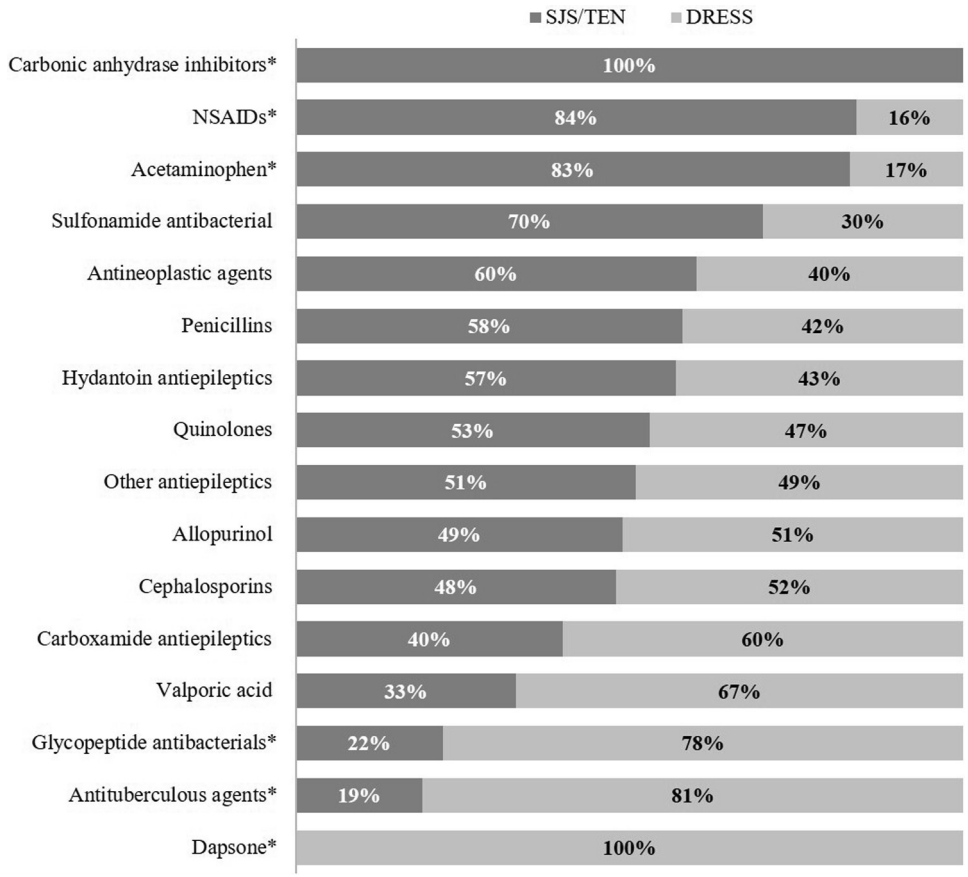

FIGURE 1. Differences in SCAR phenotypes according to the causative pharmacological groups (N ≥ 10). Carbonic anhydrase inhibitors, acetazolamide and methazolamide; Sulfonamide antibacterial, sulfamethoxazole/trimethoprim; Hydantoin antiepileptics, phenytoin and fosphenytoin; Other antiepileptics, classified as N03AX by Anatomical Therapeutic Chemical classification system; Carboxamide antiepileptics, carbamazepine and oxcarbazepine; Glycopeptide antibacterials, vancomycin and teicoplanin. *DRESS*, Drug reaction with eosinophilia and systemic symptoms; *NSAID*, nonsteroidal anti-inflammatory drug; *SCAR*, severe cutaneous adverse reaction; *SJS*, Stevens-Johnson syndrome; *TEN*, toxic epidermal necrolysis. *$P < .01$.

together. Phenotypic differences of SCARs in various drug groups showed that carbonic anhydrase inhibitors, NSAIDs, and acetaminophen predominantly cause SJS/TEN, whereas dapsone, glycopeptide antibacterials, and antituberculous agents mainly cause DRESS. SJS/TEN and DRESS were both mediated by drug-specific T cells, and this finding may be an important clue in understanding which immunological factors contribute to the development of different phenotypes.[39] Given that some specific HLA alleles show associations with certain phenotypes of SCARs, analyzing their impact on the phenotypes could shed light on the pathogenesis of SCARs.

The time interval from the first drug intake to the onset of symptoms was previously known to be 4 to 28 days in SJS/TEN and 2 to 6 weeks in DRESS.[2] These time intervals varied depending not only on the phenotype of SCARs but also on the causative drugs.[14,15] The onset of SJS/TEN occurred 19 days (7-31 days) and 13 days (7-27 days) after the first intake of the 2 major causative drugs addressed in our study, allopurinol and carbamazepine, respectively. However, in patients with DRESS, the onset of symptoms was observed 29 days (20-36 days) and 32 days (21-40 days) after the first intake of allopurinol and carbamazepine, respectively. The RegiSCAR study showed similar latent periods with these drugs: 20 days (14-32 days) for allopurinol and 15 days (12-20 days) for carbamazepine in SJS/TEN,[14] and 20 days (17-30 days) for allopurinol and 29 days (20-36 days) for carbamazepine in DRESS.[15]

Most of the patients with SCAR were admitted for the management of reaction. Because about half of the patients with SCAR were admitted via the emergency department, medical staff of the emergency department should be well aware of SCAR. Our results showed higher inpatient SCAR cases compared with those observed in the RegiSCAR study.[15] It was found that 23.3% of DRESS occurred in hospitalized patients.

The long-term sequelae of SCARs varied depending on the study[40-43] and have been reported to be up to 65% in SJS/TEN and 11.5% in DRESS.[2] However, in our study, long-term sequelae occurred at lower frequencies as compared with previous studies, at 13% in SJS/TEN and 3% in DRESS. The mortality rates of our patients with SCAR were 8.9% in SJS/TEN and 4.2% in DRESS, which were slightly lower than the 10% to 40% in SJS/TEN and 5% to 10% in DRESS reported in recent SCAR studies.[2,3,5,17,41,44] However, studies in China (SJS/TEN 5.4% and DRESS <1%)[37,38] and Malaysia (total SCAR 5.8%)[45] have reported lower mortality rates than those found in our study.

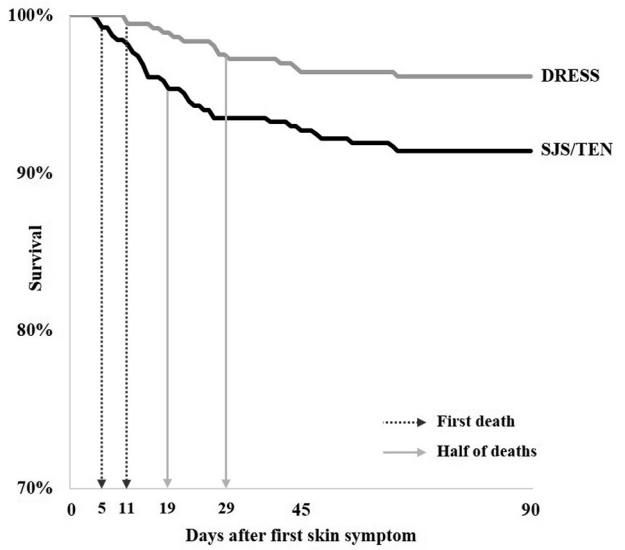

FIGURE 2. Survival of patients with SCAR according to the disease phenotype. *DRESS*, Drug reaction with eosinophilia and systemic symptoms; *SCAR*, severe cutaneous adverse reaction; *SJS*, Stevens-Johnson syndrome; *TEN*, toxic epidermal necrolysis.

In terms of the time of death, approximately 90% of deaths from SCARs occurred within 2 months of the time frame of the study. The mortality rates of SJS/TEN and DRESS were 8.6% and 3.9%, respectively, on the 90th day of the study, and 8.9% and 4.2%, respectively, at the end of 1 year. In the RegiSCAR study, the all-cause mortality of SJS/TEN was 28% on the 90th day and 34% at the end of 1 year.[44] It was difficult to directly compare the mortality rate observed in our study and the RegiSCAR study, due to differences in the study population and design. Nevertheless, the likelihood of the decline of death overtime after the high mortality rate in the early period is observed in both studies.

Morbidity and mortality differed according to the causative drug. The type of causative drug itself may affect the clinical course and the prognosis of SCAR.[3,46-50] However, the outcome may also be influenced by the age and the underlying medical conditions associated with the use of causative drugs.[34,47,51]

This registry likely included most SCAR cases in Korea during the study period because almost all tertiary hospitals in Korea participated in the registry. Besides registry studies, several studies using individual case safety reports or national health data have been attempted.[18,20,52] Our study showed a similar pattern of causative drugs as other Korean SCAR studies using different data sources,[4,53] supporting the validity of our data. To overcome the inherent limitations of the data-driven study,[54] various attempts have been made recently to extract large amounts of medical data more effectively.[55-57] SCAR research is likely to progress further in the near future due to the advancement in medical informatics.

This study was limited by its retrospective design, which resulted in the lack of standardized protocol and datasets such as scheduled laboratory tests, skin biopsies, genetic tests, and follow-up of patients. The study was also limited by the lack of confirmatory tests for the causative drug. In some cases, determining a single causative agent was difficult, but the rechallenge was contraindicative due to safety and ethical concerns. Patch tests or intradermal tests were performed only in a specific group of patients. Therefore, the most probable culprit drug was registered as the cause of each case through causality assessments by reviewing medical records and follow-up reports. To overcome these limitations, an expanded prospective registry with the standardized investigation and bio-sample collection will be required.

CONCLUSION

In the nationwide SCAR registry in Korea, the leading causative drugs of SCARs were allopurinol and carbamazepine, followed by vancomycin and antituberculous agents. Some drugs preferentially caused a specific phenotype of SCAR. The overall mortality rate of SCARs was 6.6%, and death mostly occurred within 2 months after the initial skin symptom.

REFERENCES

1. Roujeau JC, Stern RS. Severe adverse cutaneous reactions to drugs. N Engl J Med 1994;331:1272-85.
2. Duong TA, Valeyrie-Allanore L, Wolkenstein P, Chosidow O. Severe cutaneous adverse reactions to drugs. Lancet 2017;390:1996-2011.
3. Mockenhaupt M. Epidemiology of cutaneous adverse drug reactions. Chem Immunol Allergy 2012;97:1-17.
4. Yang MS, Lee JY, Kim J, Kim GW, Kim BK, Kim JY, et al. Incidence of Stevens-Johnson syndrome and toxic epidermal necrolysis: a nationwide population-based study using National Health Insurance Database in Korea. PLoS One 2016;11:e0165933.
5. Cacoub P, Musette P, Descamps V, Meyer O, Speirs C, Finzi L, et al. The DRESS syndrome: a literature review. Am J Med 2011;124:588-97.
6. Yang MS, Kim JY, Kang MG, Lee SY, Jung JW, Cho SH, et al. Direct costs of severe cutaneous adverse reactions in a tertiary hospital in Korea. Korean J Intern Med 2019;34:195-201.
7. Kelly JP, Auquier A, Rzany B, Naldi L, Bastuji-Garin S, Correia O, et al. An international collaborative case-control study of severe cutaneous adverse reactions (SCAR). Design and methods. J Clin Epidemiol 1995;48:1099-108.
8. Chung WH, Hung SI, Hong HS, Hsih MS, Yang LC, Ho HC, et al. Medical genetics: a marker for Stevens-Johnson syndrome. Nature 2004;428:486.
9. Lonjou C, Thomas L, Borot N, Ledger N, de Toma C, LeLouet H, et al. A marker for Stevens-Johnson syndrome ...: ethnicity matters. Pharmacogenomics J 2006;6:265-8.
10. Jung JW, Kim JY, Park IW, Choi BW, Kang HR. Genetic markers of severe cutaneous adverse reactions. Korean J Intern Med 2018;33:867-75.
11. Bastuji-Garin S, Rzany B, Stern RS, Shear NH, Naldi L, Roujeau JC. Clinical classification of cases of toxic epidermal necrolysis, Stevens-Johnson syndrome, and erythema multiforme. Arch Dermatol 1993;129:92-6.
12. Kardaun SH, Sidoroff A, Valeyrie-Allanore L, Halevy S, Davidovici BB, Mockenhaupt M, et al. Variability in the clinical pattern of cutaneous side-effects of drugs with systemic symptoms: does a DRESS syndrome really exist? Br J Dermatol 2007;156:609-11.
13. Edwards IR, Biriell C. Harmonisation in pharmacovigilance. Drug Saf 1994;10:93-102.
14. Mockenhaupt M, Viboud C, Dunant A, Naldi L, Halevy S, Bouwes Bavinck JN, et al. Stevens-Johnson syndrome and toxic epidermal necrolysis: assessment of medication risks with emphasis on recently marketed drugs. The EuroSCAR-study. J Invest Dermatol 2008;128:35-44.
15. Kardaun SH, Sekula P, Valeyrie-Allanore L, Liss Y, Chu CY, Creamer D, et al. Drug reaction with eosinophilia and systemic symptoms (DRESS): an original multisystem adverse drug reaction. Results from the prospective RegiSCAR study. Br J Dermatol 2013;169:1071-80.
16. Halevy S, Ghislain PD, Mockenhaupt M, Fagot JP, Bouwes Bavinck JN, Sidoroff A, et al. Allopurinol is the most common cause of Stevens-Johnson syndrome and toxic epidermal necrolysis in Europe and Israel. J Am Acad Dermatol 2008;58:25-32.
17. Diphoorn J, Cazzaniga S, Gamba C, Schroeder J, Citterio A, Rivolta AL, et al. Incidence, causative factors and mortality rates of Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) in northern Italy: data from the REACT registry. Pharmacoepidemiol Drug Saf 2016;25:196-203.

18. Sousa-Pinto B, Araujo L, Freitas A, Correia O, Delgado L. Stevens-Johnson syndrome/toxic epidermal necrolysis and erythema multiforme drug-related hospitalisations in a national administrative database. Clin Transl Allergy 2018;8:2.
19. Miliszewski MA, Kirchhof MG, Sikora S, Papp A, Dutz JP. Stevens-Johnson syndrome and toxic epidermal necrolysis: an analysis of triggers and implications for improving prevention. Am J Med 2016;129:1221-5.
20. Abe J, Umetsu R, Mataki K, Kato Y, Ueda N, Nakayama Y, et al. Analysis of Stevens-Johnson syndrome and toxic epidermal necrolysis using the Japanese Adverse Drug Event Report database. J Pharm Health Care Sci 2016;2:14.
21. Rodriguez-Martin S, Martin-Merino E, Lerma V, Rodriguez-Miguel A, Gonzalez O, Gonzalez-Herrada C, et al. Active surveillance of severe cutaneous adverse reactions: a case-population approach using a registry and a health care database. Pharmacoepidemiol Drug Saf 2018;27:1042-50.
22. Wang YH, Chen CB, Tassaneeyakul W, Saito Y, Aihara M, Choon SE, et al. The medication risk of Stevens-Johnson syndrome and toxic epidermal necrolysis in Asians: the major drug causality and comparison with the US FDA label. Clin Pharmacol Ther 2019;105:112-20.
23. Yang MS, Kang MG, Jung JW, Song WJ, Kang HR, Cho SH, et al. Clinical features and prognostic factors in severe cutaneous drug reactions. Int Arch Allergy Immunol 2013;162:346-54.
24. Lee KW, Oh DH, Lee C, Yang SY. Allelic and haplotypic diversity of HLA-A, -B, -C, -DRB1, and -DQB1 genes in the Korean population. Tissue Antigens 2005;65:437-47.
25. Shim JS, Yun J, Kim MY, Chung SJ, Oh JH, Kang DY, et al. The presence of HLA-B75, DR13 homozygosity, or DR14 additionally increases the risk of allopurinol-induced severe cutaneous adverse reactions in HLA-B*58:01 carriers. J Allergy Clin Immunol Pract 2019;7:1261-70.
26. Kim SH, Lee KW, Song WJ, Kim SH, Jee YK, Lee SM, et al. Carbamazepine-induced severe cutaneous adverse reactions and HLA genotypes in Koreans. Epilepsy Res 2011;97:190-7.
27. Kang HR, Jee YK, Kim YS, Lee CH, Jung JW, Kim SH, et al. Positive and negative associations of HLA class I alleles with allopurinol-induced SCARs in Koreans. Pharmacogenet Genomics 2011;21:303-7.
28. Peter JG, Lehloenya R, Dlamini S, Risma K, White KD, Konvinse KC, et al. Severe delayed cutaneous and systemic reactions to drugs: a global perspective on the science and art of current practice. J Allergy Clin Immunol Pract 2017;5:547-63.
29. Papay J, Yuen N, Powell G, Mockenhaupt M, Bogenrieder T. Spontaneous adverse event reports of Stevens-Johnson syndrome/toxic epidermal necrolysis: detecting associations with medications. Pharmacoepidemiol Drug Saf 2012;21:289-96.
30. Micheletti RG, Chiesa-Fuxench Z, Noe MH, Stephen S, Aleshin M, Agarwal A, et al. Stevens-Johnson syndrome/toxic epidermal necrolysis: a multicenter retrospective study of 377 adult patients from the United States. J Invest Dermatol 2018;138:2315-21.
31. Rodriguez-Martin S, Martin-Merino E, Lerma V, Rodriguez-Miguel A, Gonzalez O, Gonzalez-Herrada C, et al. Incidence of Stevens-Johnson syndrome/toxic epidermal necrolysis among new users of different individual drugs in a European population: a case-population study. Eur J Clin Pharmacol 2019;75:237-46.
32. Hiransuthikul A, Rattananupong T, Klaewsongkram J, Rerknimitr P, Pongprutthipan M, Ruxrungtham K. Drug-induced hypersensitivity syndrome/drug reaction with eosinophilia and systemic symptoms (DIHS/DRESS): 11 years retrospective study in Thailand. Allergol Int 2016;65:432-8.
33. Shu C, Shu D, Tie D, Yu M, Zhang R, Wang T, et al. Toxic epidermal necrolysis induced by methazolamide in a Chinese-Korean man carrying HLA-B*59:01. Int J Dermatol 2015;54:1242-5.
34. Kim S, Yun J, Kang DY, Park HJ, Jo EJ, Jung JW, et al. Carbonic anhydrase inhibitor-induced Stevens-Johnson syndrome/toxic epidermal necrolysis leads to extensive cutaneous involvement. J Allergy Clin Immunol Pract 2019;7:2851-2853.e2.
35. Kim SH, Lee SK, Kim SH, Park HW, Chang YS, Lee KW, et al. Antituberculosis drug-induced hypersensitivity syndrome and its association with human leukocyte antigen. Tuberculosis (Edinb) 2013;93:270-4.
36. Konvinse KC, Trubiano JA, Pavlos R, James I, Shaffer CM, Bejan CA, et al. HLA-A*32:01 is strongly associated with vancomycin-induced drug reaction with eosinophilia and systemic symptoms. J Allergy Clin Immunol 2019;144:183-92.
37. Wang L, Mei XL. Drug reaction with eosinophilia and systemic symptoms: retrospective analysis of 104 cases over one decade. Chin Med J (Engl) 2017;130:943-9.
38. Yang SC, Hu S, Zhang SZ, Huang JW, Zhang J, Ji C, et al. The epidemiology of Stevens-Johnson syndrome and toxic epidermal necrolysis in China. J Immunol Res 2018;2018:4320195.
39. Chen CB, Abe R, Pan RY, Wang CW, Hung SI, Tsai YG, et al. An updated review of the molecular mechanisms in drug hypersensitivity. J Immunol Res 2018;2018:6431694.
40. White KD, Abe R, Ardern-Jones M, Beachkofsky T, Bouchard C, Carleton B, et al. SJS/TEN 2017: building multidisciplinary networks to drive science and translation. J Allergy Clin Immunol Pract 2018;6:38-69.
41. Hsu DY, Brieva J, Silverberg NB, Silverberg JI. Morbidity and mortality of Stevens-Johnson syndrome and toxic epidermal necrolysis in United States adults. J Invest Dermatol 2016;136:1387-97.
42. Yang CW, Cho YT, Chen KL, Chen YC, Song HL, Chu CY. Long-term sequelae of Stevens-Johnson syndrome/toxic epidermal necrolysis. Acta Derm Venereol 2016;96:525-9.
43. Chen YC, Chang CY, Cho YT, Chiu HC, Chu CY. Long-term sequelae of drug reaction with eosinophilia and systemic symptoms: a retrospective cohort study from Taiwan. J Am Acad Dermatol 2013;68:459-65.
44. Sekula P, Dunant A, Mockenhaupt M, Naldi L, Bouwes Bavinck JN, Halevy S, et al. Comprehensive survival analysis of a cohort of patients with Stevens-Johnson syndrome and toxic epidermal necrolysis. J Invest Dermatol 2013;133:1197-204.
45. Loo CH, Tan WC, Khor YH, Chan LC. A 10-years retrospective study on severe cutaneous adverse reactions (SCARs) in a tertiary hospital in Penang, Malaysia. Med J Malaysia 2018;73:73-7.
46. Sim DW, Yu JE, Jeong J, Jung JW, Kang HR, Kang DY, et al. Variation of clinical manifestations according to culprit drugs in DRESS syndrome. Pharmacoepidemiol Drug Saf 2019;28:840-8.
47. Park HJ, Yun J, Kang DY, Park JW, Koh YI, Kim S, et al. Unique clinical characteristics and prognosis of allopurinol-induced severe cutaneous adverse reactions. J Allergy Clin Immunol Pract 2019;7:2739-2749.e3.
48. Lee HK, Yoon KC, Seo KY, Ueta M, Kim MK. Chronic ocular complications of Stevens-Johnson syndrome associated with causative medications in Korea. J Allergy Clin Immunol Pract 2018;6:700-702.e2.
49. Park CS, Kang DY, Kang MG, Kim S, Ye YM, Kim SH, et al. Severe cutaneous adverse reactions to antiepileptic drugs: a nationwide registry-based study in Korea. Allergy Asthma Immunol Res 2019;11:709-22.
50. Lee SY, Nam YH, Koh YI, Kim SH, Kim S, Kang HR, et al. Phenotypes of severe cutaneous adverse reactions caused by nonsteroidal anti-inflammatory drugs. Allergy Asthma Immunol Res 2019;11:212-21.
51. Oh HL, Kang DY, Kang HR, Kim S, Koh YI, Kim SH, et al. Severe cutaneous adverse reactions in Korean pediatric patients: a study from the Korea SCAR Registry. Allergy Asthma Immunol Res 2019;11:241-53.
52. Velasco-Tirado V, Alonso-Sardon M, Cosano-Quero A, Romero-Alegria A, Sanchez-Los Arcos L, Lopez-Bernus A, et al. Life-threatening dermatoses: Stevens-Johnson Syndrome and toxic epidermal necrolysis. Impact on the Spanish public health system (2010-2015). PLoS One 2018;13:e0198582.
53. Kang MG, Sohn KH, Kang DY, Park HK, Yang MS, Lee JY, et al. Analysis of individual case safety reports of severe cutaneous adverse reaction in Korea. Yonsei Med J 2019;60:208-15.
54. Chiriac AM, Macy E. Large health system databases and drug hypersensitivity. J Allergy Clin Immunol Pract 2019;7:2125-31.
55. Fukasawa T, Takahashi H, Kameyama N, Fukuda R, Furuhata S, Tanemura N, et al. Development of an electronic medical record-based algorithm to identify patients with Stevens-Johnson syndrome and toxic epidermal necrolysis in Japan. PLoS One 2019;14:e0221130.
56. Wolfson AR, Zhou L, Li Y, Phadke NA, Chow OA, Blumenthal KG. Drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome identified in the electronic health record allergy module. J Allergy Clin Immunol Pract 2019;7:633-40.
57. Yang MS, Lee JY, Kim J, Kim GW, Kim BK, Kim JY, et al. Searching for the culprit drugs for Stevens-Johnson syndrome and toxic epidermal necrolysis from a nationwide claim database in Korea. J Allergy Clin Immunol Pract 2020;8:690-695.e2.

ONLINE REPOSITORY

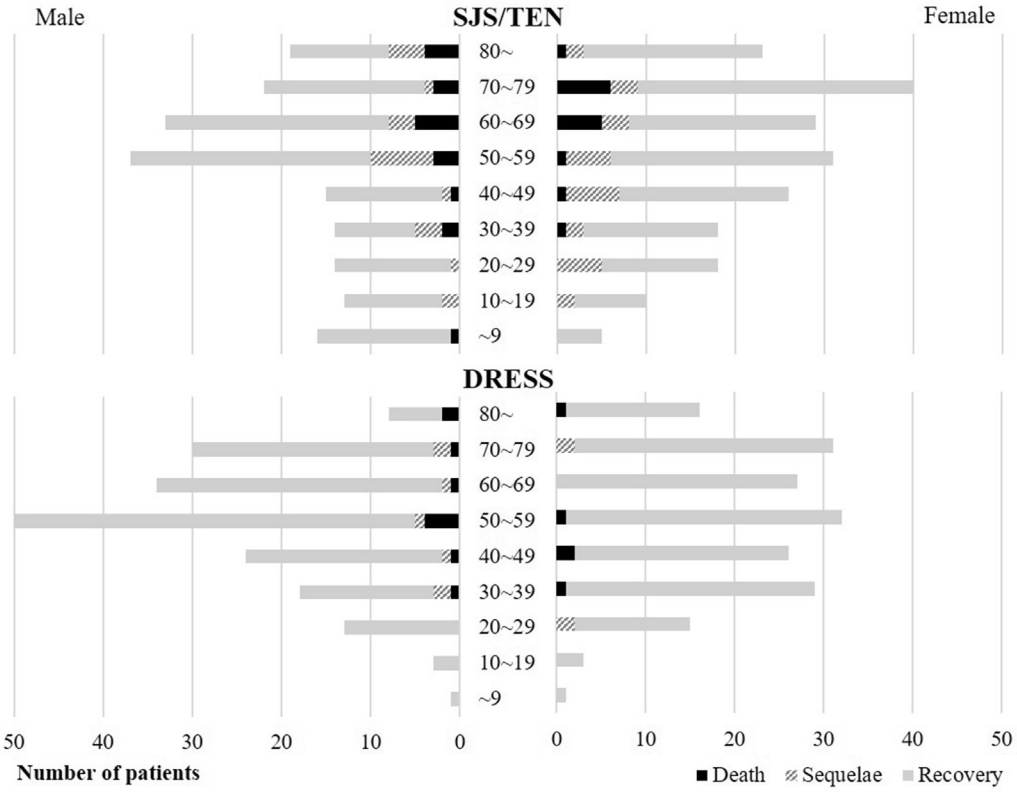

FIGURE E1. Age distribution of patients with SCAR in Korea. *DRESS*, Drug reaction with eosinophilia and systemic symptoms; *SCAR*, severe cutaneous adverse reaction; *SJS*, Stevens-Johnson syndrome; *TEN*, toxic epidermal necrolysis.

TABLE E1. The number of cases according to causative drugs of SCARs

					RegiSCAR score of DRESS cases			
	Drugs	Total	SJS/TEN	DRESS	3	4	5	6
1	Allopurinol	104	51	53	21	20	9	3
2	Carbamazepine	71	28	43	17	14	7	5
3	Vancomycin	35	8	27	8	10	9	
4	Lamotrigine	25	15	10	4	4	1	1
5	Acetaminophen	24	20	4	2	1	1	
	Amoxicillin	24	19	5	3	2		
7	Ceftriaxone	22	9	13	6	6	1	
	Isoniazid	22	6	16	6	8	2	
9	Cefaclor	16	13	3	1	1	1	
10	Dapsone	15	0	15	2	7	4	2
	Valproic acid	15	5	10	5	4	1	
12	Ciprofloxacin	14	7	7	2	2	3	
13	Phenytoin	13	7	6	3	2	1	
14	Ibuprofen	12	12	0				
	Piperacillin/tazobactam	12	5	7	2	2	3	
	Rifampicin	12	3	9	4	3	2	
17	Loxoprofen	11	8	3	1	2		
18	Sulfamethoxazole/trimethoprim	10	7	3	1	1		1
19	Levofloxacin	9	5	4	1	1	2	
	Methazolamide	9	9	0				
21	Aceclofenac	8	6	2			2	
	Levetiracetam	8	1	7	3	4		
23	Cefotaxime	7	1	6	2	3	1	
	Ethambutol	7	0	7	4	2	1	
	Sulfasalazine	7	3	4	1	3		
26	Gabapentin	6	3	3	1	1	1	
	Nafcillin	6	1	5	2	3		
	Pyrazinamide	6	0	6	3	2	1	
29	Celecoxib	5	1	4	1	2	1	
	Dexibuprofen	5	5	0				
	Mefenamic acid	5	5	0				
	Meropenem	5	1	4	1	2	1	
33	Cefazedone	4	3	1		1		
	Doxycycline	4	3	1		1		
	Methotrexate	4	3	1			1	
	Moxifloxacin	4	1	3	1	2		
	Phenobarbital	4	2	2	1	1		
	Zaltoprofen	4	3	1		1		
39	Aspirin	3	2	1		1		
	Azithromycin	3	1	2	1	1		
	Cefepime	3	1	2	1	1		
	Cefpiramide	3	0	3	2	1		
	Cefpodoxime	3	2	1		1		
	Cefuroxime	3	1	2	1	1		
	Cimetidine	3	3	0				
	Meloxicam	3	3	0				
	Roxithromycin	3	3	0				
	Talniflumate	3	3	0				
49	Acetazolamide	2	2	0				
	Cefalexin	2	2	0				
	Cefditoren pivoxil	2	0	2	1	1		
	Cefixime	2	2	0				
	Cefotetan	2	0	2	1	1		

(continued)

TABLE E1. *(Continued)*

					RegiSCAR score of DRESS cases			
	Drugs	Total	SJS/TEN	DRESS	3	4	5	6
	Ceftazidime	2	1	1	1			
	Deflazacort	2	2	0				
	Diazepam	2	1	1			1	
	Doxorubicin	2	1	1		1		
	Famotidine	2	0	2	1	1		
	Fenofibrate	2	1	1	1			
	Flomoxef	2	1	1		1		
	Indobufen	2	1	1				1
	Lithium	2	0	2	2			
	Naproxen	2	2	0				
	Nortriptyline	2	1	1		1		
	Oxcarbazepine	2	1	1			1	
	Pantoprazole	2	0	2	1	1		
	Penicillamine	2	1	1	1			
	Propylthiouracil	2	1	1	1			
	Temozolomide	2	2	0				
	Ticarcillin	2	0	2	2			
	Zonisamide	2	2	0				
72	Acetyl-L-carnitine	1	0	1	1			
	Acyclovir	1	1	0				
	Ampicillin	1	1	0				
	Atorvastatin	1	1	0				
	Balofloxacin	1	1	0				
	Boceprevir	1	0	1	1			
	Buspirone	1	0	1		1		
	Cefatrizine	1	1	0				
	Cefcapene pivoxil	1	1	0				
	Cefodizime	1	0	1	1			
	Cefoperazone	1	0	1	1			
	Cefotiam	1	0	1		1		
	Cefprozil	1	0	1	1			
	Ceftizoxime	1	0	1		1		
	Cephalexin	1	1	0				
	Cimetropium bromide	1	1	0				
	Cisplatin	1	1	0				
	Clarithromycin	1	1	0				
	Clindamycin	1	0	1		1		
	Clobetasol propionate	1	1	0				
	Cloxacillin	1	1	0				
	Dacarbazine	1	1	0				
	Diclofenac	1	1	0				
	Diltiazem	1	1	0				
	Docetaxel	1	1	0				
	Doxofylline	1	1	0				
	Econazole	1	1	0				
	Entecavir	1	1	0				
	Eperisone	1	0	1				1
	Escitalopram	1	0	1		1		
	Esomeprazole	1	0	1			1	
	Fluconazole	1	1	0				
	Fosphenytoin	1	1	0				
	Furosemide	1	1	0				
	Gimeracil/tegafur/oteracil	1	0	1		1		

(continued)

TABLE E1. *(Continued)*

					RegiSCAR score of DRESS cases			
	Drugs	Total	SJS/TEN	DRESS	3	4	5	6
	Imipenem	1	0	1	1			
	Itraconazole	1	1	0				
	Lansoprazole	1	1	0				
	Levodropropizine	1	1	0				
	Loperamide	1	1	0				
	Methimazole	1	1	0				
	Metolazone	1	0	1	1			
	Metronidazole	1	1	0				
	Nabumetone	1	1	0				
	Nicorandil	1	0	1	1			
	Norfloxacin	1	1	0				
	Ofloxacin	1	1	0				
	Oxaliplatin	1	0	1		1		
	P-Aminosalicylic calcium	1	0	1	1			
	Penicillin	1	0	1	1			
	Pentazocine	1	0	1	1			
	Piperacillin/sulbactam	1	1	0				
	Pitavastatin	1	1	0				
	Prednisolone	1	1	0				
	Pseudoephedrine	1	1	0				
	Quetiapine	1	0	1		1		
	Rabeprazole	1	1	0				
	Ramipril	1	1	0				
	Ranitidine	1	0	1	1			
	Risperidone	1	1	0				
	Ropivacaine	1	0	1	1			
	Sorafenib tosylate	1	0	1			1	
	Streptokinase	1	1	0				
	Streptomycin	1	0	1		1		
	Sulodexide	1	0	1	1			
	Teicoplanin	1	0	1		1		
	Terbinafine	1	1	0				
	Thalidomide	1	0	1	1			
	Tinidazole	1	1	0				
	Tiropramide	1	0	1		1		
	Tobramycin	1	1	0				
	Torasemide	1	1	0				
	Tranexamic acid	1	1	0				
	Vemurafenib	1	0	1	1			
	Warfarin	1	1	0				
	Influenza vaccine	1	1	0				
148	<Health supplement>							
	Ginkgo	1	1	0				
	Gum nutrition	1	0	1	1			
	Omega-3	1	1	0				
	Protein	1	0	1		1		
	Traditional Chinese medicine	2	1	1		1		
149	<Unspecified>							
	Combined cold medicine	4	4	0				
	Unspecified NSAIDs	4	4	0				
	Unspecified antibiotics	2	2	0				
	Unspecified medication	3	3	0				

DRESS, Drug reaction with eosinophilia and systemic symptoms; *NSAID*, nonsteroidal anti-inflammatory drug; *SCAR*, severe cutaneous adverse reaction; *SJS*, Stevens-Johnson syndrome; *TEN*, toxic epidermal necrolysis.

TABLE E2. Drugs related to cases with sequelae

Case no.	Drugs most suspected as culprit	Other suspected drug
1	Allopurinol	Ciprofloxacin, pregabalin
2	Allopurinol	Colchicine, loxoprofen
3	Allopurinol	Loxoprofen
4	Allopurinol	
5	Allopurinol	
6	Allopurinol	
7	Allopurinol	
8	Carbamazepine	
9	Carbamazepine	
10	Carbamazepine	
11	Carbamazepine	
12	Carbamazepine	
13	Carbamazepine	
14	Acetaminophen	Levodropropizine, pseudoephedrine
15	Acetaminophen	Amoxicillin
16	Acetaminophen	
17	Acetaminophen	
18	Acetaminophen	
19	Amoxicillin	Acetaminophen, loxoprofen, eperisone
20	Amoxicillin	Cephradine, mefenamic acid
21	Amoxicillin	Loxoprofen, pseudoephedrine
22	Amoxicillin	Acetaminophen
23	Ibuprofen	Acetaminophen, azithromycin, tramadol
24	Ibuprofen	
25	Ibuprofen	
26	Ciprofloxacin	Dexibuprofen
27	Ciprofloxacin	Itraconazole
28	Dapsone	Cephradine
29	Dapsone	
30	Isoniazid	Ethambutol, rifampicin, pyrazinamide
31	Isoniazid	Rifampicin, ethambutol, pyrazinamide
32	Lamotrigine	Valproic acid, propranolol, donepezil, clonazepam, mirtazapine
33	Lamotrigine	
34	Methazolamide	Dexibuprofen
35	Methazolamide	
36	Vancomycin	
37	Vancomycin	
38	Aceclofenac	Allopurinol
39	Acetazolamide	
40	Cefaclor	Acetaminophen, ibuprofen, levodropropizine
41	Ceftriaxone	Vancomycin, teicoplanin
42	Cefuroxime	
43	Celecoxib	
44	Deflazacort	Amlodipine
45	Dexibuprofen	Cefditoren
46	Diclofenac	Loxoprofen, cefaclor
47	Fluconazole	
48	Gabapentin	
49	Levofloxacin	Loxoprofen, mefenamic acid
50	Mefenamic acid	
51	Moxifloxacin	
52	Phenytoin	
53	Piperacillin/tazobactam	Levofloxacin
54	Propylthiouracil	Ciprofloxacin, mefenamic acid

(continued)

TABLE E2. *(Continued)*

Case no.	Drugs most suspected as culprit	Other suspected drug
55	Ramipril	
56	Roxithromycin	
57	Sulfamethoxazole/trimethoprim	
58	Sulfasalazine	
59	Tranexamic acid	
60	Valproic acid	Naproxen, amoxicillin, loxoprofen
61	Zonisamide	

TABLE E3. Drugs related to deceased cases

Case no.	Drugs most suspected as culprit	Other suspected drug
1	Allopurinol	Furosemide
2	Allopurinol	Colchicine
3	Allopurinol	
4	Allopurinol	
5	Allopurinol	
6	Allopurinol	
7	Allopurinol	
8	Allopurinol	
9	Allopurinol	
10	Allopurinol	
11	Allopurinol	
12	Vancomycin	Meropenem, ampicillin
13	Vancomycin	Piperacillin/tazobactam, levofloxacin
14	Vancomycin	Meropenem
15	Vancomycin	
16	Isoniazid	Rifampicin, ethambutol, pyrazinamide, cefaclor
17	Isoniazid	Pyrazinamide, ethambutol, moxifloxacin
18	Isoniazid	Ethambutol, rifampicin, pyrazinamide
19	Valproic acid	Meropenem, vancomycin
20	Valproic acid	
21	Valproic acid	
22	Cefaclor	
23	Cefaclor	
24	Ciprofloxacin	Loxoprofen
25	Ciprofloxacin	
26	Levofloxacin	Piperacillin/tazobactam
27	Levofloxacin	
28	Aceclofenac	Isoniazid, rifampicin, ethambutol, levofloxacin
29	Amoxicillin	
30	Carbamazepine	
31	Cefalexin	Amikacin, cefazedone
32	Cefpiramide	Pentazocine, levofloxacin, meropenem
33	Ceftazidime	
34	Entecavir	
35	Esomeprazole	
36	Lamotrigine	Piroxicam, diclofenac, vancomycin
37	Lansoprazole	Oxycodone, levosulpiride, aspirin
38	Meropenem	Vancomycin, pantoprazole, isoniazid, rifampicin, pyrazinamide
39	Methazolamide	
40	Methotrexate	
41	Naproxen	Dexibuprofen
42	Ofloxacin	Levofloxacin
43	Pantoprazole	
44	Penicillamine	Nifedipine
45	Phenobarbital	
46	Piperacillin/tazobactam	Vancomycin, fluconazole
47	Rifampicin	Ethambutol, pyrazinamide, isoniazid
48	Sulfamethoxazole/trimethoprim	
49	Temozolomide	