Allergy Asthma Immunol Res. 2019 Sep;11(5):709-722
https://doi.org/10.4168/aair.2019.11.5.709
pISSN 2092-7355·eISSN 2092-7363

Allergy, Asthma & Immunology Research AAIR

Original Article

Severe Cutaneous Adverse Reactions to Antiepileptic Drugs: A Nationwide Registry-Based Study in Korea

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Received: Feb 5, 2019
Revised: May 25, 2019
Accepted: Jun 3, 2019

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Disclosure

None of the authors has any conflict of interest to disclose. We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines. None of the authors has any conflict of interest to disclose.

ABSTRACT

Purpose: Severe cutaneous adverse reactions (SCARs), including Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), and drug reaction with eosinophilia and systemic symptoms (DRESS) to antiepileptic drug (AED), are rare, but result in significant morbidity and mortality. We investigated the major culprit drugs, clinical characteristics, and clinical course and outcomes of AED-induced SCARs using a nationwide registry in Korea.
Methods: A total of 161 patients with AED-induced SCARs from 28 referral hospitals were analyzed. The causative AEDs, clinical characteristics, organ involvements, details of treatment, and outcomes were evaluated. We compared the clinical and laboratory parameters between SJS/TEN and DRESS according to the leading causative drugs. We further determined risk factors for prolonged hospitalization in AED-induced SCARs.
Results: Carbamazepine and lamotrigine were the most common culprit drugs causing SCARs. Valproic acid and levetiracetam also emerged as the major causative agents. The disease duration and hospital stay in carbamazepine-induced SJS/TEN were shorter than those in other AEDs ($P< 0.05$, respectively). In younger patients, lamotrigine caused higher incidences of DRESS than other drugs ($P= 0.045$). Carbamazepine, the most common culprit drug for SCARs, was associated with a favorable outcome related with prolonged hospitalization in SJS (odds ratio, 0.12; 95% confidence interval, 0.02-0.63, $P= 0.12$), and thrombocytopenia was found to be a risk factor for prolonged hospitalization in DRESS.
Conclusion: This was the first large-scale epidemiological study of AED-induced SCARs in Korea. Valproic acid and levetiracetam were the significant emerging AEDs causing SCARs in addition to the well-known offending AEDs such as carbamazepine and lamotrigine. Carbamazepine was associated with reduced hospitalization, but thrombocytopenia was a risk factor for prolonged hospitalization. Our results suggest that the clinical characteristics and clinical courses of AED-induced SCARs might vary according to the individual AEDs.

Keywords: Antiepileptic drugs; Stevens-Johnson syndrome; toxic epidermal necrolysis

INTRODUCTION

Patients receiving antiepileptic drugs (AEDs) suffer from various adverse drug reactions (ADRs).[1,2] Most of these ADRs are type A, which are acute and related to the pharmacologic properties of the drugs. They usually develop after the initiation of a drug or during dose escalation and typically decrease over time or after dose reduction. On the other hand, unpredictable and idiosyncratic type B reactions occur in 3%–10% of the patients treated with AEDs, which range from mild maculopapular eruptions to serious and life-threatening severe cutaneous adverse drug reactions (SCARs), such as Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), and drug reaction with eosinophilia and systemic symptoms (DRESS).[3,4] They usually arise during the first few weeks of treatment and can be reversed after discontinuation of the offending drug. Delayed recognition and intervention can increase the risk of morbidity and mortality.[5] Aromatic anticonvulsants, including phenytoin (PHT), phenobarbital (PHB), and carbamazepine (CBZ), are the most common AEDs casing various cutaneous hypersensitivity reactions including SCARs.[6,7] Recently, lamotrigine (LTG) which is structurally different from other aromatic AEDs, have also been reported to cause skin rashes and even SCARs.[8,9]

https://doi.org/10.4168/aair.2019.11.5.709

ADRs to AEDs are the leading causes of treatment failure and are strong predictors of impaired health-related quality of life in patients with epilepsy, independent of seizure outcomes.[4] Although non-serious drug eruptions are relatively frequent with AEDs, the incidence of SCARs with AEDs is known to be 1–10 in 10,000 patients.[10] Despite a low incidence rate, the mortality rate of SJS/TEN and the DRESS is 10%–40%. Moreover, unnecessary hospitalization and extension of hospital stay by SCARs are often unavoidable, resulting in a significantly higher medical expense. Therefore, AED-induced SCARs are a significant burden not only from the medical point of view but also from the socioeconomic aspects.[11,12]

Although several published reports are describing the clinical characteristics, causative agents, and risk factors of AED-induced SJS/TEN and DRESS,[2,6,10,13,14] there have been quite a few reports to date comparing the differences between SJS/TEN and DRESS. The variation in the incidence and risk factors of SCARs among different ethnic populations across their genetic constitutions have been reported.[15] Therefore, it is relevant and necessary to perform comprehensive studies on the characteristics of AED-induced SCARs in Asian countries including Korea.

In this study, we investigated the major culprit drugs, clinical characteristics, and clinical courses and outcomes of AED-induced SCARs comparing the similarities and differences between AED-induced SJS/TEN and DRESS using a nationwide SCARs registry in Korea.

MATERIALS AND METHODS

Data collection and study subjects

A web-based Korean SCARs registry was built in 2014. This registry was based on the Regional Pharmacovigilance Center (RPVC) pilot project of the Korean Food and Drug Administration (KFDA) which has played a crucial role in the Korean Pharmacovigilance System Administration.[16] Thirty-six general hospitals, including 27 RPVC, participated in the Korean SCARs registry, which was opened for enrollment of the SCAR cases occurring between 2010 and 2015. All physicians involved in maintaining the registry were allergy specialists. We have evaluated the medical history, offending drugs, and causal relationships between the drugs and the reactions in each hospital and reported the information to the registry. This study was approved by the Institutional Review Board committee of each participating study center (Hallym University Dongtan Sacred Heart Hospital, HDT 2016-01-001, *etc.*).

The diagnosis of SJS and TEN was based on the diagnostic criteria proposed by the RegiSCAR study group.[17] SJS/TEN is characterized by widespread exanthema or blisters with skin detachment of < 10% of the body surface area (BSA) in SJS, 10%–29% in an overlap of SJS/TEN, and > 30% in TEN. The inclusion criteria of DRESS were a suspected drug reaction with an acute skin rash, the involvement of at least 1 internal organ, abnormalities in blood parameters including the elevation of liver enzyme, leukocytosis, atypical lymphocytosis or eosinophilia, and a body temperature > 38°C. The patients who met ≥3 of these criteria were considered DRESS.[18] In all cases, causality evaluation using the World Health Organization-Uppsala Monitoring Centre (WHO-UMC) causality assessment system was performed, and 'certain,' 'probable,' and 'possible' cases were recruited.[19,20] Total of 745 SCAR cases were registered; 384 cases of SJS or TEN, and 361 cases of DRESS.[21] Among 1,393 drugs suspected

https://doi.org/10.4168/aair.2019.11.5.709

as culprit drugs, main causative agents of SCARs in Korea were allopurinol (13.8%), carbamazepine (9.3%), and vancomycin (4.7%). We enrolled a total of 161 patients with AED-induced SCARs, which account for 21.6% of all SCARs cases. Data from the included patients treated with AEDs including CBZ, PHT, LTG, PHB, valproic acid (VPA), fosphenytoin, levetiracetam (LEV), zonisamide, and oxcarbazepine (OXC) were obtained. The names of the offending AEDs, clinical manifestations, hospital courses, time intervals from the onset of symptoms to the day of resolve/discharge (disease duration), time intervals from the drug exposure to the onset of symptoms (latent period), organ involvements, laboratory data, complications, and outcomes were all analyzed.

Statistical analyses

The data are represented as the mean ± standard deviation (SD) if normally distributed, or the median and range if otherwise. The differences in the characteristics of the study participants were compared across subgroups with the χ^2 test or Fisher's exact test for the categorical variables, and analysis of variance with Scheffé's *post-hoc* test or Kruskal-Wallis test with Dunn's *post-hoc* test for the continuous variables, as applicable. Normality tests for distribution of data were performed using Shapiro-Wilk's test. Univariate and multivariate logistic regression analyses were performed to identify prognostic factors which were independently associated with prolonged hospitalizations. A multivariate model was created using a backward elimination method, and the probability was set at 0.05 for removal. Odds ratio (OR) with 95% confidence interval (CI) were calculated for prognostic factors associated with prolonged hospitalizations. All statistical analyses were performed with SPSS version 24.0 (SPSS Inc., Chicago, IL, USA), and a *P* value of < 0.05 was considered statistically significant.

RESULTS

Demographic data

The demographic characteristics of the study subjects are summarized (**Table 1**). Among 161 patients with ADE-induced SCARs, 56 had SJS (34.87%), 16 had TEN (n = 5) + SJS/TEN overlap (n = 11) (9.9%), and 89 had DRESS (55.3%). There were no significant differences in the age of onset and sex among the 3 groups. The latent period tended to be longer in DRESS (33 ± 26.6 days) than in the other 2 groups (29.6 ± 33.2 days in SJS, 29.5 ±17.7 days in TEN + SJS/TEN overlap, $P = 0.201$). The median duration of the disease was 23.7 days, and there was no significant difference among the 3 groups. We have further investigated information about past exposure drugs and found that 4 people had been prescribed the same medication as the causative drug of SCARs (3 for carbamazepine, 1 for levetiracetam), except for one who has inaccurate information. The underlying allergic diseases, such as asthma, allergic rhinitis, atopic dermatitis, and drug allergy; and comorbidities, such as diabetes mellitus, hypertension, liver diseases, chronic kidney diseases, rheumatic diseases, and infections were similar between the groups. Interestingly, the malignancy rates were higher in SJS (14.3%) and TEN + SJS/TEN overlap (23.1%) than in DRESS (6.4%), without any significant difference ($P = 0.083$). Among a total of 15 patients with malignancy, six patients had a brain tumor, and one patient had brain metastasis from lung cancer. They took AEDs to prevent seizure. The rest of the patients were prescribed AEDs for pain control (n = 4), seizure control (n = 2), and spasm control (n = 1). One patient could not determine the reason.

https://doi.org/10.4168/aair.2019.11.5.709

Table 1. The baseline characteristics of patients

Characteristics	Overall	SJS	TEN + SJS/TEN overlap	DRESS	*P* value
All patients	161 (100.0)	56 (34.8)	16 (9.9)	89 (55.3)	
Age (yr)	51.6 ± 18.3	53.1 ± 20.0	51.4 ± 15.4	50.6 ± 17.8	0.573
< 20	10 (6.2)	5 (8.9)	0 (0.0)	5 (5.6)	0.754
20–39	32 (19.9)	9 (16.1)	3 (18.8)	20 (22.5)	
40–59	65 (40.4)	20 (35.7)	8 (50.0)	37 (41.6)	
≥ 60	54 (33.5)	22 (39.3)	5 (31.3)	27 (30.3)	
Sex					0.572
Male	79 (49.1)	27 (48.2)	6 (37.5)	46 (51.7)	
Female	82 (50.9)	29 (51.8)	10 (62.5)	43 (48.3)	
Latent period (day)	31.5 ± 29.0 (0–182)	29.6 ± 33.2 (0–182)	29.5 ± 27.0 (1–100)	33.0 ± 26.6 (0–177)	0.201
Disease duration (day)	23.7 ± 16.5 (4–104)	21.1 ± 9.2 (4–54)	33.4 ± 24.6 (10–91)	23.5 ± 17.7 (4–104)	0.135
Allergic disease					
Asthma	3 (2.3)	1/45 (2.2)	0/10 (0.0)	2/77 (2.6)	1.000
Allergic rhinitis	3 (2.3)	2/45 (4.4)	0/10 (0.0)	1/78 (1.3)	0.647
Atopic dermatitis	0 (0.0)	0/43 (0.0)	0/10 (0.0)	0/77 (0.0)	-
Drug allergy	11 (9.3)	5/38 (13.2)	1/11 (9.1)	5/69 (7.2)	0.569
Previous antiepileptic drug exposure	5 (4.6)	1/43 (2.3)	0/11 (0.0)	4/55 (7.3)	0.514
Diabetes mellitus	21 (15.0)	6/49 (12.2)	3/13 (23.1)	12/78 (15.4)	0.557
Hypertension	46 (31.7)	16/49 (32.7)	4/12 (33.3)	26/84 (31.0)	0.963
Liver disease	4 (2.8)	1/49 (2.0)	0/12 (0.0)	3/81 (3.7)	1.000
Chronic kidney disease	6 (4.3)	1/49 (2.0)	1/11 (9.1)	4/81 (4.9)	0.399
Rheumatic disease	2 (1.5)	0/45 (0.0)	0/10 (0.0)	2/76 (2.6)	0.598
Infection	23 (16.8)	10/46 (21.7)	3/12 (25.0)	10/79 (12.7)	0.272
Malignancy	15 (10.7)	7/49 (14.3)	3/13 (23.1)	5/78 (6.4)	0.083

Values are expressed as number (%) or mean ± standard deviation (range).
SJS, Stevens-Johnson syndrome; TEN, toxic epidermal necrolysis; DRESS, drug reaction with eosinophilia and systemic symptoms.

Offending drugs for AED-induced SCARs

In all the cases of SCARs, CBZ was the most common offending drug, followed by LTG, VPA, PHT, and LEV (**Figure**). In the 56 cases of SJS, 28 (50%) were caused by CBZ, followed by LTG (21.4%), PHT (16.1%), VPA (12.5%), and LEV (3.6%). Similarly, CBZ was the most common causative drug in TEN + SJS/TEN overlap, followed by LTG, VPA. In the 89 cases of DRESS, 48 (53.9%) were caused by CBZ, followed by VPA (15.7%), LTG (14.6%), LEV (10.1%), and PHT (7.9%). Most of SJS and TEN were caused by CBZ, LTG, and VPA, whereas DRESS was caused by CBZ, VPA, and LTG, respectively.

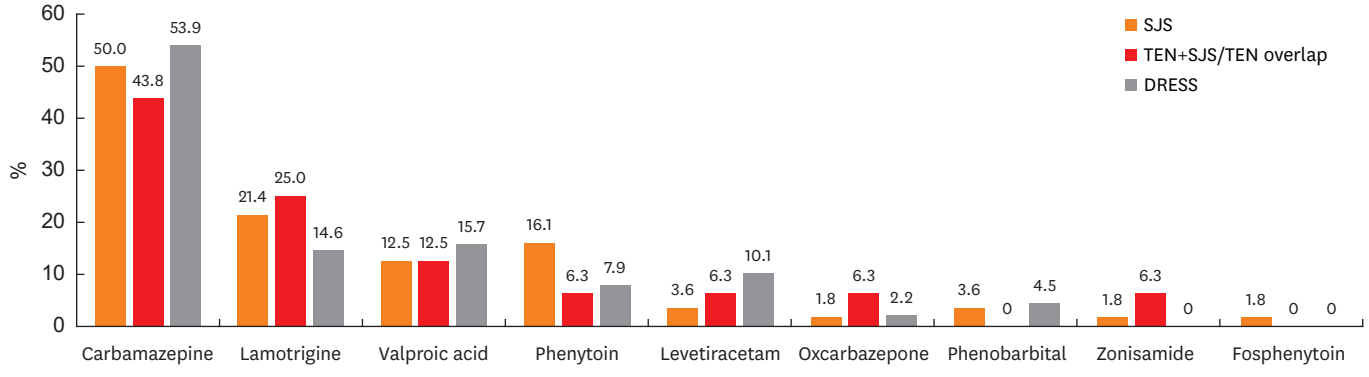

Figure. Causative drugs of SJS, TEN+SJS/TEN overlap, and DRESS.
SJS, Stevens-Johnson syndrome; TEN, toxic epidermal necrolysis; DRESS, drug reaction with eosinophilia and systemic symptoms.

https://doi.org/10.4168/aair.2019.11.5.709

Clinical manifestations and laboratory findings of AED-induced SCARs

The clinical features and laboratory findings of the included patients are summarized in **Table 2**. Fever at presentation was more frequently found in DRESS than in the other 2 groups, without statistical significance (70.8% in DRESS, 53.7% in SJS, 68.8% in TEN + SJS/TEN, $P = 0.110$). Most of the patients had various types of cutaneous involvements. Skin detachment was significantly increased in TEN + SJS/TEN overlap (62.5%) compared to SJS (26.8%) and DRESS (6.7%). In a *post hoc* analysis, there were significant differences between the 3 groups. Vesicle/bullae, Nikolsky's sign, and mucosa involvement also showed significant differences, respectively. There was no difference between SJS and TEN + SJS/TEN, while there was a statistical difference between these 2 groups and DRESS in the *post hoc* analysis. In laboratory findings, the proportion of leukocytosis, atypical lymphocytosis, hepatic involvement, and renal involvement were more increased in DRESS than in the other 2 groups, without statistical differences ($P > 0.05$, respectively). On the other hand, peak leukocytosis, peak eosinophilia, and lymphadenopathy showed significant differences among the 3 groups ($P < 0.05$, respectively); however, statistical significance were shown only between the SJS and DRESS groups in the *post hoc* analysis. Eosinophilia and peak alanine transferase (ALT) level showed a significant difference among the 3 groups, while *post hoc* analyses did not show any significant differences.

Treatment and outcomes in AED-induced SCARs

We classified the treatment options into 4 categories: conservative care, systemic corticosteroids, intravenous immunoglobulin (IVIG), and a combination of a systemic corticosteroid and IVIG (**Table 3**). Fourteen patients (9.3%) were managed only with conservative care. Nine patients were treated with antihistamines, and 1 patient was provided a topical steroid. Others had inaccurate information. The percentage of patients treated with

Table 2. Clinical manifestations and laboratory findings

Characteristics	Overall	SJS	SJS/TEN overlap	DRESS	*P* value	*Posthoc**
All patients, No. (%)	161 (100.0)	56 (34.8)	16 (9.9)	89 (55.3)		
Fever	103 (64.8)	29/54 (53.7)	11/16 (68.8)	63/89 (70.8)	0.110	
Duration (day) (min–max)	5.6 ± 8.0 (1–60)	5.1 ± 5.1 (1–20)	11.4 ± 17.0 (1–60)	4.7 ± 6.0 (1–33)	0.213	
Cutaneous involvement						
Erythema	156 (96.9)	54/56 (96.4)	16/16 (100.0)	86/89 (96.6)	1.000	
Targetoid lesion	20 (12.4)	9/56 (16.1)	3/16 (18.8)	8/89 (9.0)	0.279	
Detachment	31 (19.3)	15/56 (26.8)	10/16 (62.5)	6/89 (6.7)	0.000	b > a > c
Vesicle/bullae	31 (19.3)	19/56 (33.9)	9/16 (56.3)	3/89 (3.4)	0.000	a = b > c
Nikolsky's sign	18 (27.3)	9/24 (37.5)	8/9 (88.9)	1/33 (3.0)	0.000	a = b > c
Mucosal involvement	78 (59.1)	49/53 (92.5)	12/13 (92.3)	17/66 (25.8)	0.000	a = b > c
Leukocytosis	60 (75.0)	15/24 (62.5)	7/11 (63.6)	38/45 (84.4)	0.088	
Peak leukocytosis	16,381 ± 9,365 (2,029–53,090)	12,861 ± 7,207 (2,029–32,000)	12,534 ± 5,650 (6,600–26,660)	19,200 ± 10,221 (4,450–53,090)	0.009	c > a
Atypical lymphocytosis	22 (42.3)	3/12 (25.0)	1/4 (25.0)	18/36 (50.0)	0.276	
Eosinophilia	80 (65.0)	19/37 (51.4)	5/10 (50.0)	56/76 (73.7)	0.037	NS
Peak eosinophil count	2,001 ± 3,445 (7–27,100)	980 ± 1,402 (49–6,009)	719 ± 788 (7–2,100)	2,667 ± 4,136 (9–27,100)	0.003	c > a
Thrombocytopenia	21 (20.8)	5/32 (15.6)	4/14 (28.6)	12/55 (21.8)	0.579	
Lymphadenopathy	14 (19.7)	1/24 (4.2)	1/8 (12.5)	12/39 (30.8)	0.019	c > a
Hepatic involvement	91 (70.5)	30/44 (68.2)	7/14 (50.0)	54/71 (76.1)	0.150	
Peak ALT (IU/L)	317.3 ± 621.3 (7–4,930)	186.7 ± 238.9 (7–1,175)	120.0 ± 99.2 (22–381)	437.2 ± 797.3 (13–4,930)	0.029	NS†
Renal involvement	31 (36.5)	5/25 (20.0)	3/11 (27.3)	23/49 (46.9)	0.058	
Peak Scr (mg/dL)	1.3 ± 1.3 (0.3–8.4)	1.0 ± 0.8 (0.3–4.5)	1.6 ± 2.3 (0.5–8.4)	1.3 ± 1.2 (0.4–5.6)	0.296	

Values are expressed as median with either range or percentage in parenthesis. Fever ≥ 38°C, leukocytosis ≥ 10,000/μL, eosinophilia ≥ 500/μL, thrombocytopenia < 100,000/μL, renal involvement (Scr ≥ 1.0 mg/dL), hepatic involvement (ALT ≥ 80 IU/L); For *post hoc* pairwise comparison for categorical variables, Bonferroni's method was applied to adjust the significance level of alpha due to the multiple testing.

SJS, Stevens-Johnson syndrome; TEN, toxic epidermal necrolysis; DRESS, drug reaction with eosinophilia and systemic symptoms; ALT, alanine transaminase; Scr, serum creatinine; NS, not significant.

*Abbreviation for *post hoc* analysis: (a) for SJS, (b) for TEN+SJS overlap, and (c) for DRESS; †*P* values derived from *post hoc* pairwise comparison were not statistically significant.

https://doi.org/10.4168/aair.2019.11.5.709

Table 3. Treatment options and outcomes

Characteristics	Overall	SJS	TEN + TEN/SJS overlap	DRESS	*P* value	*Posthoc*[†]
Treatment options						
Conservative	14 (9.3)	1/56 (1.8)	0/15 (0.0)	13/80 (16.3)	0.007	c > a
Corticosteroids[*]						
Use	141 (89.2)	54/56 (96.4)	16/16 (100.0)	71/86 (82.6)	0.013	a > c
Duration (day)	27.2 ± 58.9 (0–379)	21.5 ± 44.9 (0–276)	25.8 ± 41.8 (0–169)	31.8 ± 70.4 (0–379)	0.352	
Maximal dose (mg/day)	60 (5–1,000)	45 (8–500)	50 (5–250)	60 (5–1,000)	0.179	
IVIG						
Use	20 (13.2)	11/56 (19.6)	5/15 (33.3)	4/80 (5.0)	0.002	a = b > c
Maximal dose (g/day)	33.8 (3.5–250)	12.0 (3.5–70)	50.0 (22.5–70)	33.8 (18.5–250)	0.360	
Both corticosteroids and IVIG	19 (12.6)	10/56 (17.9)	5/15 (33.3)	4/80 (5.0)	0.003	a = b > c
Hospital course and outcome						
Development during admission	23 (14.6)	4/54 (7.4)	3/16 (18.8)	16/87 (18.4)	0.150	
Hospitalization period (days)	20.2 ± 20.3	17.0 ± 12.1	31.7 ± 27.1	20.2 ± 22.4	0.030	b > c
ICU transfer	6 (4.0)	0/55 (0.0)	2/16 (12.5)	4/78 (5.1)	0.038	NS[‡]
Clinical outcome						
Recovery	142 (88.8)	47 (83.9)	10 (66.7)	85 (95.5)	0.002	c > b
Sequelae	12 (7.5)	7 (12.5)	3 (20.0)	2 (2.2)	0.006	NS
Skin	9 (75.0)	6/7 (85.7)	2/3 (66.7)	1/2 (50.0)	0.714	
Eye	4 (33.3)	1/7 (14.3)	2/3 (66.7)	1/2 (50.0)	0.265	
Death	6 (3.8)	2 (3.6)	2 (13.3)	2 (2.2)	0.168	

For *post hoc* pairwise comparison for categorical variables, Bonferroni's method was applied to adjust the significance level of alpha due to the multiple testing.
ICU, intensive care unit; IVIG, intravenous immunoglobulin.
[*]Corticosteroids dose: equivalent to prednisolone; [†]Abbreviation for post-hoc analysis: (a) for SJS, (b) for TEN+SJS overlap, and (c) for DRESS; [‡]*P* values derived from post-hoc pairwise comparison were not statistically significant.

conservative care was higher in DRESS than in SJS ($P = 0.007$). The majority of SCAR patients (89.2%) received systemic corticosteroids. The frequency of use of systemic corticosteroids was higher in SJS than in DRESS (96.4% vs. 82.6%, $P = 0.013$). A total of 20 patients were treated with IVIG in addition to corticosteroid. The frequency of use of IVIG was higher in both SJS and TEN + SJS/TEN overlap than in DRESS.

The duration of hospital stay was significantly longer in the TEN + SJS/TEN overlap group than in the DRESS group, whereas the recovery rate was significantly higher in the DRESS than in TEN + SJS/TEN overlap. Most of the patients recovered fully, but twelve patients had sequelae. The overall mortality rate was 3.8% (6 out of 161), and higher mortality was observed in TEN + SJS/TEN overlap (13.3%), followed by SJS (3.8%) and DRESS (2.2%). According to the causative drug for mortality, VPA was the most common drug causing death (3 out of 6 deaths), followed by PHB, CBZ, and LTG (1 death each).

Comparison between the clinical course and outcomes of SCARs according to the culprit drugs

We tried to evaluate the differences in the clinical characteristics and outcomes against major culprit drugs, including CBZ, LTG, VPA, PHT, and LTV. Patients were re-classified into 2 groups as SJS/TEN and DRESS because of the limitation of case number (**Tables 4** and **5**). In SJS/TEN, the latent period and disease duration were shorter with CBZ than with the other AEDs ($P = 0.039$), while *post hoc* analyses did not show any significant differences. The length of drug administration in SJS/TEN was remarkably shorter with CBZ than with VPA ($P = 0.047$, *post hoc* analysis). On the other hand, in DRESS, the age of onset was significantly lower with LTG as compared to CBZ ($P = 0.026$, *post hoc* analysis). There was no significant difference in the latent period or disease duration between the drugs. Although there was no statistical significance in a *post hoc* analysis, the length of hospital stay in VPA- and PHT-induced DRESS was prolonged ($P = 0.027$).

https://doi.org/10.4168/aair.2019.11.5.709

Table 4. Clinical course and outcomes in SJS/TEN according to the major causative drugs

Characteristics	Carbamazepine (n = 35)	Lamotrigine (n = 16)	Valproic acid (n = 9)	Phenytoin (n = 10)	Levetiracetam (n = 3)	*P* value
Age (yr)	54 (15–81)	56 (15–69)	56 (15–70)	68 (2–84)	48 (37–83)	0.587
Female	17 (48.6)	9 (56.3)	6 (66.7)	5 (50.0)	1 (33.3)	0.836
Latent period (day)	14 (0–151)	28 (3–182)	27 (0–182)	31 (19–91)	41 (22–47)	0.039*
Disease duration (day)	18 (4–91)	23 (12–91)	19 (6–91)	27 (16–35)	27 (27–31)	0.038*
Admission duration (day)	14 (0–88)	20 (0–103)	42 (8–103)	21 (6–31)	17 (13–28)	0.035†
Intensive care unit care	1 (2.9)	0 (0.0)	1 (11.1)	0 (0.0)	0 (0.0)	0.435
Clinical outcome						
Recovery	31 (88.6)	12 (80.0)	4 (44.4)	8 (80.0)	3 (100.0)	0.065
Sequelae	4 (11.4)	2 (13.3)	2 (22.2)	2 (20.0)	0 (0.0)	0.827
Skin	3 (75.0)	2 (100.0)	1 (50.0)	2 (100.0)	-	1.000
Eye	2 (50.0)	0 (0.0)	1 (50.0)	0 (0.0)	-	0.600
Death	0 (0.0)	1 (6.7)	3 (33.3)	0 (0.0)	0 (0.0)	0.010

Values are expressed as median with range or number (%).
SJS, Stevens-Johnson syndrome; TEN, toxic epidermal necrolysis.
*No significant difference by Dunn's *post hoc* test; †Significant difference between carbamazepine and valproic acid (Dunn's *post hoc* test, $P = 0.047$).

Table 5. Clinical manifestations according to major causative drugs in DRESS

Characteristics	Carbamazepine (n = 48)	Lamotrigine (n = 13)	Valproic acid (n = 14)	Phenytoin (n = 7)	Levetiracetam (n = 9)	*P* value
Age (yr)	56 (15–89)	36 (9–61)	55 (1–77)	47 (39–72)	49 (25–76)	0.045*
Female	21 (43.8)	9 (69.2)	6 (42.9)	3 (42.9)	3 (33.3)	0.484
Latent period (day)	33 (1–177)	18 (7–91)	31 (11–38)	24 (1–38)	36 (1–104)	0.236
Disease duration (day)	18 (4–93)	17 (6–46)	27 (10–104)	18 (12–104)	18 (10–104)	0.441
Admission duration (day)	12 (0–87)	11 (0–44)	25 (8–142)	26 (10–142)	13 (8–142)	0.027†
Intensive care unit care	3 (6.7)	0 (0.0)	1 (7.7)	0 (0.0)	0 (0.0)	1.000
Clinical outcome						
Recovery	45 (93.8)	13 (100.0)	14 (100.0)	7 (100.0)	9 (100.0)	1.000
Sequelae	2 (4.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1.000
Skin	1 (50.0)	-	-	-	-	-
Eye	1 (50.0)	-	-	-	-	-
Death	1 (2.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1.000

Values are expressed as median with range or number (%).
DRESS, drug reaction with eosinophilia and systemic symptoms.
*Significant difference between lamotrigine and carbamazepine (Dunn's *post hoc* test, $P = 0.026$); †No significant difference by Dunn's *post hoc* test.

Prognostic factors of AED-induced SCAR

We evaluated the risk factors for prolonged hospitalization (> 3 weeks) (**Supplementary Table S1**). Fever and use of VPA were significantly associated with prolonged hospitalization in both SJS/TEN and DRESS. Leukocytosis and infections were shown as poor prognostic factors in SJS/TEN, while thrombocytopenia was significantly associated with prolonged hospitalization in DRESS. In the multivariate analysis, CBZ was found to be negatively associated with prolonged hospitalization in SJS (OR, 0.08; 95% CI, 0.01–0.78; $P = 0.03$). On the other hand, thrombocytopenia was significantly associated with prolonged hospitalization in DRESS (OR, 6.52; 95% CI, 1.02–41.81; $P = 0.048$) (**Table 6**).

DISCUSSION

We found that CBZ, LTG, VPA, PHT, and LEV were the most common culprit drugs causing SCARs in Korea. The proportion of each phenotype of SCARs did not show any significant difference across the individual AEDs; although there was no difference in statistical analysis, the proportion of LEV-induced DRESS was higher than that of SJS/TEN by LEV(**Supplementary Table S2**). The overall mortality rates were 3.8%, accounting for 3.6%

https://doi.org/10.4168/aair.2019.11.5.709

Table 6. Risk factor analysis for prolonged hospitalization in SCARs

Variable	Multivariate analysis	
	OR (95% CI)	*P* value
SJS		
Carbamazepine		
Yes	0.08 (0.01–0.78)	0.030
No	1.00	
DRESS		
Thrombocytopenia		
Yes	6.52 (1.02–41.81)	0.048
No	1.00	

SCAR, severe cutaneous adverse drug reaction; SJS, Stevens-Johnson syndrome; DRESS, drug reaction with eosinophilia and systemic symptoms; OR, odds ratio; CI, confidence interval.

in SJS, 13.3% in TEN + SJS/TEN overlap, and 2.2% in DRESS. Interestingly, CBZ, which is the most common causative agent, was a good prognostic factor for prolonged hospitalization. Besides, thrombocytopenia was a risk factor for prolonged hospitalization in DRESS. SCARs are rarely occurring drug hypersensitivity reactions, and the use of the antiepileptic drug is not common. Thus, this study has provided us with insightful data on AED-induced SCARs in Korea.

Both DRESS and SJS/TEN are T cell-mediated delayed hypersensitivity reactions. The clinical manifestations of SCARs typically occur within 1–12 weeks after initiating drug therapy.[3,17,22,23] In a recent study, the average latent period in AED-induced SCARs was found to be around 31 days (range 0–182 days), which is similar to other previous studies.[24] Therefore, it is necessary to monitor the clinical symptoms and laboratory reports for at least 1 month after initiating AEDs because early diagnosis and withdrawal of the culprit drug are essential to improve the outcome in drug hypersensitivity reactions, especially SCARs.

Our results have shown that more than 50% of both SJS and TEN + SJS/TEN overlap group had eosinophilia. Twenty-five percent of patients with SJS and TEN+ SJS/TEN overlap had atypical lymphocytosis. Moreover, a considerable number of SJS/TEN patients also had hepatic and renal involvements. Similarly, approximately 26% of the DRESS patients had mucosal involvement, which is a characteristic feature of SJS/TEN. Therefore, our results support the previous reports that both SJS/TEN and DRESS share some clinical and laboratory features.[22,25,26] These findings suggest that some patients might have both the diseases co-existing at the same time. Further studies are needed to evaluate the frequency of patients having common clinical features of both the diseases and the underlying mechanism of their co-existence.

Aromatic AEDs, including PHT, CBZ, PHB, and LTG, are classified as high-risk drugs for ADRs and also are the primary offenders causing SCARs. In the present study, CBZ and LTG were the most common offending drugs causing SCARs, which is consistent with the previous studies where aromatic AEDs including PHT, CBZ, PHB, and LTG are classified as high-risk drugs for ADRs and also are the primary offenders causing SCARs.[6,27] We have also found that VPA and LEV more commonly caused SCARs in the Korean population. Hypersensitivity reactions have been rarely observed in patients taking non-aromatic AEDs, such as VPA, LEV, and vigabatrin.[8,28-30] It has been reported that the incidence of LTG-induced hypersensitivity was increased when VPA and/or other AEDs are administered concurrently.[31] In this study, a total of 13 (8%) patients were treated with different AEDs as combination therapies. Among them, VPA was the most commonly used drug, accounting for 69% (9/13) in the combination

https://doi.org/10.4168/aair.2019.11.5.709

regimen (5 with LTG, 2 with PHT, 1 with LEV, and 1 with PTB). It should be, however, noted that there was a considerable number of SCARs caused by VPA monotherapy.

LEV is a new-generation AED having a chemical structure different from the conventional AEDs, and its use has rapidly increased in recent years. Several cases of LEV-induced hypersensitivity reactions have been reported, although it is generally well tolerated.[32,33] In our study, a total of 12 (7.5%) LEV-induced SCARs was reported. It might be explained by the fact that non-aromatic AED-induced SCARs might be associated with some specific HLA genotypes in the Korean population like with CBZ. Therefore, LEV-induced SCARs need to be continuously monitored and studied.

The mortality rate of SCARs has been reported to be 10%–40% ranging from approximately 10% in SJS to > 30% in TEN.[34] Recently, in the United States, the mean adjusted mortality rates were found to be 4.8% for SJS and 14.8% for TEN between 2009 to 2012.[35] Similarly, a recent study using a national medical insurance review system database in Korea have shown that the in-patient mortality was 5.7% in DRESS and 15.7% in SJS/TEN.[36] Our data showed that the mortality rate in DRESS, SJS, and TEN + SJS/TEN overlap was 2.2%, 3.6%, and 13.3%, respectively. Although some recent studies have shown reduced mortality rates, our results demonstrated especially lower mortality rate in TEN + SJS/TEN overlap than the previous reports.[33,35,37]

Until now, there are no established therapies for SCARs. The previous results from a RegiSCAR cohort could not confirm the beneficial effects of systemic corticosteroids on reducing mortality in SCARs.[38] A recent meta-analysis, however, showed that corticosteroids and cyclosporine were associated with a decreased mortality rate as compared to a supportive treatment in SJS/TEN.[39] In the present study, the majority of patients were treated with systemic corticosteroids, and a total of 13.2% of patients were treated with IVIG. Although a randomized controlled trial is lacking and there is much controversy regarding the benefits of IVIG, our results suggest that IVIG or the combination of corticosteroids and IVIG might reduce the mortality rate in SCARs

In our study, VPA was detected as the third most frequent AED causing SCARs, and all deaths were associated with VPA monotherapy. In addition, VPA was associated with prolonged hospitalization in SJS/TEN, suggesting that VPA might be related to more severe disease and poorer outcomes in the Korean population. Interestingly, the latent period, disease duration, and hospital stay with CBZ were shorter in SJS/TEN than in other drugs reflecting a better prognosis. The age of onset of LTG-induced DRESS was significantly earlier than the other drugs. The progress and prognosis of SCARs varied according to each AED, and further studies are needed to elucidate these results.

The prognostic factors of SCARs are not well established. Until now, in addition to the SCORe of Toxic Epidermal Necrosis (SCORTEN), various laboratory parameters including hypernatremia, serum lactate dehydrogenase, and thrombocytopenia are suggested to be prognostic factors in SJS/TEN.[22,40-42] In DRESS, the prognostic factors are also much less established. In DRESS, various clinical manifestations, such as tachycardia, tachypnea, and gastrointestinal bleeding; multiple underlying diseases; and abnormal laboratory findings, such as eosinophilia, reactivation of human herpesvirus 6 (HHV-6), pancytopenia, coagulopathy, and leukocytosis at presentation are considered.[22,43-45] Thrombocytopenia is known as one of the hematologic manifestations in DRESS. It is also included in the

https://doi.org/10.4168/aair.2019.11.5.709

diagnostic criteria presented by ResiSCARs (European registration of SCARs).[46] Various visceral involvements, including gastrointestinal (GI) bleeding and the hemophagocytic syndrome, were reported in DRESS.[47] Therefore, coagulopathy associated with thrombocytopenia may affect the prognosis for DRESS syndrome. Large-scale studies are needed to support this finding. Remarkably, the risk of prolonged hospitalization (> 3 weeks) decreased in CBZ-induced SJS in the present study. The mean hospitalization period in CBZ-induced SCARs was 15.6 days in SJS/TEN and 16.1 days in DRESS, which were around 4 days shorter than the mean hospitalization period of 20.2 days. To date, carbamazepine has been recognized as a critical risk factor for SCARs.[6,27,48,49] In a retrospective study using health insurance data for elderly Korean patients, CBZ was reported to increase the incidence of SCARs by about ten times.[27] However, there have been no reports that CBZ-induced SCARs have a good prognosis compared to all AED-induced SCARs as in this study. It is a remarkable result that CBZ is a negative risk factor for the length of hospitalization. Those can be explained by the fact that 1) CBZ is known to cause SCARs well so that clinicians can detect it early and promptly stop the medication, and 2) indeed, the severity of CBZ-induced SCARs may be less severe than SCARs by other AEDs.

There are several limitations to the present study. There were limited data with missing values in some patients. Notably, we could not analyze the SCORTEN score and HHV-6 reactivation in this study. Because the majority of patients were treated in various departments, they have not been adequately assessed and tested in the beginning. Secondly, there were also the possibilities of selection bias and wrong identification of the offending drug. Despite a thorough check, we could not obtain the detailed history of pre-existing diseases and co-medications used in the patients included. Thirdly, we could not verify the SCARs incidences because hospitals that have prescribed causative drugs are different from those that enrolled in the study. Also, it was hard to know the frequency of nationwide prescriptions unless we look for the data from the Korea Insurance Corporation. Also, there might be AED-induced SCAR patients missing from this study.

In conclusion, this is the first large-scale nationwide study of AED-induced SCARs in Korea, investigating prognostic factors as well as clinical characteristics common causative drugs and clinical courses. CBZ and LTG are the most common culprit drugs in SCARs, and VPA and LEV have emerged as the major causative agents. VPA was associated with a higher mortality rate. CBZ was correlated negatively with prolonged hospitalization in SJS, while thrombocytopenia is a risk factor for prolonged hospitalization in DRESS. Further studies will be needed with a more substantial cohort of AED-induced SCARs to clarify drug-specific characteristics and prognoses.

ACKNOWLEDGMENTS

This study was supported by a grant from The Korean Academy of Asthma, Allergy, and Clinical Immunology (2017) and the Ministry of Food and Drug Safety to the regional pharmacovigilance center in 2018.

SUPPLEMENTARY MATERIALS

Supplementary Table S1

Univariate analysis of risk factor analysis for prolonged hospitalization in SCARs

Click here to view

Supplementary Table S2

Comparison of causative agents between SJS/TEN and DRESS groups

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