Clinical Features and Prognostic Factors in Severe Cutaneous Drug Reactions

Min-Suk Yang^{a, b} Min-Gyu Kang^b Jae-Woo Jung^{b, c} Woo-Jung Song^b
Hye-Ryun Kang^{b, c} Sang-Heon Cho^{b, c} Kyung-Up Min^b

^aDepartment of Internal Medicine, SMG-SNU Boramae Medical Center, ^bDepartment of Internal Medicine, Seoul National University College of Medicine, and ^cDrug Safety Monitoring Center, Seoul National University Hospital, Seoul, Republic of Korea

Key Words

Stevens-Johnson syndrome · Toxic epidermal necrolysis · Drug hypersensitivity · Demography · Prognosis · Hospitalization

Abstract

Background: Severe cutaneous adverse reactions (SCARs) include Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), and drug reaction with eosinophilia and systemic symptoms (DRESS). SJS and TEN (SJS/TEN) and DRESS are thought to be different diseases; however, they share some clinical and laboratory features. Although SCORTEN serves as an excellent prognostic marker for SJS/TEN, there is still a need for development of other prognostic markers for SCARs. **Methods:** The study population consisted of 88 SCAR patients. Clinical characteristics and clinical manifestations were compared between SJS/TEN and DRESS. Risk factor analyses for prolonged hospitalization were performed. **Results:** Of the 88 patients, 41 were SJS/TEN and 47 were DRESS. Mortality rates of TEN and DRESS were 9.8 and 2.1%, respectively. Allopurinol and carbamazepine were the most common causes of both SJS/TEN and DRESS (34.7 and 62.9%, respectively). Some of the systemic presentations, such as fever and laboratory abnormalities were common in

both phenotypes. Thrombocytopenia tended to be related to prolonged hospitalization (longer than 3 weeks) in SJS/TEN (odds ratio, OR = 5.1, 95% confidence interval, CI 0.8–31.8, $p = 0.076$). In DRESS patients, leukocytosis at presentation (OR 4.8, 95% CI 1.1–20.3, $p = 0.03$) was related to prolonged hospitalization. **Conclusions:** Clinical features of SCARs in a tertiary hospital in Korea were similar to those reported previously. SJS/TEN and DRESS shared some clinical and laboratory features. Thrombocytopenia for SJS/TEN and leukocytosis at presentation for DRESS may be useful prognostic markers for prolonged hospitalization.

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Introduction

Severe cutaneous adverse reaction (SCAR) is a very rare condition and is mostly related to medication. Several delayed-type drug hypersensitivity reactions are categorized as SCARs, including Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), and drug reaction with eosinophilia and systemic symptoms (DRESS). SJS and TEN (SJS/TEN) are characterized by acute-onset blistering skin lesions and differentiated only by the extent of skin detachment. SJS/TEN is frequently accompa-

Fig. 1. Process for identifying SCAR patients using electronic medical records.

nied by fever and nonspecific hematological abnormalities such as anemia and lymphocytopenia, as well as skin detachment and mucosal involvement [1]. DRESS usually includes skin eruption and systemic symptoms, such as fever, eosinophilia and internal organ damage [2]. Although SJS/TEN and DRESS are distinct diseases, both are thought to be T cell-mediated delayed-type hypersensitivities and share some clinical characteristics, such as causative agents [3, 4]. However, the reasons for the different responses to the same drugs are not yet clear.

SCARs have significant morbidity and mortality. The mortality rate of SJS is 10%, of TEN is 30%, and of DRESS is about 10% [5]. Hospitalization and prolonged systemic corticosteroid therapy are needed in many cases. SCORTEN is the most frequently used scoring system to predict the prognosis of SJS/TEN. Other parameters, such as serum sodium, bicarbonate and lactate dehydrogenase levels, have been proposed to reflect the prognosis of SJS/TEN [6–8]. In contrast, there are no proven prognostic markers for DRESS, except that described in a recent report [9]. In this study, we analyzed the medical records of SCAR patients to evaluate the similarities and differences between SJS/TEN and DRESS, and to search for prognostic markers.

Materials and Methods

Study Subjects

Patients who visited or were admitted to Seoul National University Hospital between January 1, 2005, and December 31, 2010, were included in this study. To identify patients with a medical history of SJS/TEN and DRESS, we developed search strategies using an electronic medical record system (fig. 1). For SJS/TEN, ICD-10 diagnostic codes for SJS (L51.1) and TEN (L51.2) were searched, and 77 patients with a diagnosis of SJS or TEN were recruited for the study. As there was no appropriate code for DRESS in ICD-10, we used a stepwise approach to clarify the diagnosis. First, all patients who consulted the Department of Allergy or Dermatology for drug eruption were screened; there was a total of 1,418 patients with suspected drug eruption. Next, we checked the responses of consultations and selected 98 that contained the terms ‘hypersensitivity’, ‘DRESS’, ‘Stevens-Johnson syndrome’, or ‘toxic epidermal necrolysis’. Diagnoses of SCARs were primarily based on clinical diagnoses by the attending physicians in charge of the patients, and we confirmed the diagnoses based on the diagnostic criteria proposed by the RegiSCAR study group on retrospective review. Briefly, for a diagnosis of SJS/TEN, patients should have been hospitalized and have had widespread exanthema with 1% or more detachment of epidermis or more than one blister and mucous membrane involvement with typical appearance of individual lesions, such as atypical flat target lesion or erythematous macules [10]. Oral mucosal involvement was defined as the presence

Table 1. Demographic and clinical characteristics of SCAR patients

	SJS/TEN (n = 41)	DRESS (n = 47)	p value
Age, years	47 (1–76)	54 (3–89)	0.04
Male	21 (51.2)	26 (48.9)	1.00
Latency period, days ^a	18 (1–64)	21.5 (1–128)	0.20
Admission delay, days ^b	5 (0–50)	4 (0–34)	0.39
Hospitalization duration, days ^c	22 (8–292)	15 (1–218)	0.42
Days on systemic corticosteroids, days ^d	16.5 (1–152)	44.5 (3–1,295)	0.004
ICU care	7 (17.1)	4 (8.5)	0.23
Clinical outcome			
Recovery	37 (90.2)	46 (97.9)	0.18
Death	4 (9.8)	1 (2.1)	0.18

Values are expressed as median with either range or percentage in parentheses.

^a Time elapsed from exposure to causative agents to the occurrence of mucocutaneous involvement; data were available for 68 patients.

^b Elapsed time from the initiation of mucocutaneous involvement to hospitalization.

^c Data were available for 87 patients.

^d Data were available for 60 patients.

of hemorrhagic bullae or erosion in buccal mucosa, tongue or lips. Any abnormalities in the eyes confirmed by ophthalmologists from vascular congestion to pseudomembrane formation were designated as ocular involvement. For DRESS, criteria proposed by Kardaun et al. [11] was adopted. There were 6 definite, 22 probable and 19 possible cases according to the criteria. Hepatic involvement was defined as more than a 2-fold increase of serum alanine transaminase levels and renal involvement was defined as more than a 1.5-fold increase of serum creatinine levels from the upper limit of the reference range or from the baseline creatinine level of the patient when the baseline creatinine level was higher than the upper limit. A total of 148 patients with SJS/TEN or DRESS were recruited after omitting duplicate cases, and 88 patients with SCARs were included in this study, after excluding 56 patients who did not satisfy the inclusion criteria (fig. 1).

Clinical Characteristics to Be Compared

In the 88 SCAR patients identified as described above, clinical characteristics such as age, gender, date of onset, admission date, hospital stay, suspected drug, time lag between exposure to the drug and onset of disease, and clinical manifestations, including mucocutaneous and systemic involvement, treatment modality and clinical outcome, were compared between SJS/TEN and DRESS. SCORTEN was calculated for SJS/TEN as previously reported [12]. In all cases, causative agents were assessed as ‘certain’ or ‘probable’ based on the WHO-UMC causality assessment system. For SJS/TEN, ALDEN scores were calculated to assess the causality of the causative agents and SJS/TEN [13].

The day on which any mucocutaneous manifestation developed was considered the date of onset. For patients who had already received systemic corticosteroids because of their underlying medical conditions (e.g. rheumatological diseases), the duration of systemic corticosteroid treatment was defined as that from

the day on which the patient received an additional dose of systemic corticosteroid because of SCAR to the day the patient returned to the baseline dose.

Statistical Analyses

Statistical analyses were performed with SPSS version 16.0 for Windows (SPSS, Chicago, Ill., USA). Data are described with the median and range because none of the variables had a normal distribution. For comparison between SJS/TEN and DRESS, the Mann-Whitney U test was used for continuous variables and the χ^2 test or Fisher’s exact test was used for categorical variables. This study was approved by the Seoul National University Hospital Institutional Review Board.

Results

Demographic and Causative Factors

Of 88 patients, 41 were diagnosed with SJS/TEN and 47 were diagnosed with DRESS. Among the SJS/TEN patients, 24 had SJS and 17 had TEN. Comparisons of demographic features between SJS/TEN and DRESS indicated significant differences in age at the time of onset and the number of days on systemic corticosteroids; there were no significant differences in other demographic features (table 1). More than 90% of both SJS/TEN and DRESS patients showed latency periods of 6 weeks or less (online suppl. fig. 1; for all online suppl. material, see www.karger.com/doi/10.1159/000354918). Three SJS/TEN patients and 1 DRESS patient developed skin lesions

Fig. 2. Causative agents for SCARs. Allopurinol and anticonvulsants were the most common causes of SCARs in Korea. Causative agents were similar for both SJS/TEN and DRESS. NSAIDs = Nonsteroidal anti-inflammatory drugs; ACE = angiotensin-converting enzyme; Tb = tuberculosis.

just 1 day after exposure, and all had shown previous reactions with similar severities. The latency period of SJS/TEN peaked on the third week, and that of DRESS peaked on the fourth week. Four (9.8%) SJS and 9 (19.1%) DRESS patients had acquired SCARs during admission for underlying medical conditions (in-hospital cases). The durations of hospitalization of SJS/TEN and DRESS patients were not significantly different. However, 9 out of 47 DRESS patients (19.1%) were hospitalized for more than 10 weeks. Mortality rates for SJS/TEN and DRESS were 9.8 and 2.1%, respectively.

Descriptions of suspected causes were found in 75 patients (30 SJS/TEN and 45 DRESS patients), and a total of 28 types of drugs were suspected as causative agents. As a group, anticonvulsants and allopurinol were the two major causes of SCARs (fig. 2). For SJS/TEN, allopurinol (16.7%) was the most common causative agent, followed by carbamazepine (10%), vancomycin (10%) and enalapril (10%). As the culprit agents were primarily inferred from the description of attending physicians and no allergy tests were performed, ALDEN scores for SJS/TEN were calculated to assure the causality. Among 29 SJS/TEN cases with available data, there were 14 very probable, 6 probable, 5 possible and 4 unlikely cases. Among the 4 unlikely cases, there were 2 enalapril-, 1 glimepiride- and 1 clonazepam-related cases. Among DRESS patients, allopurinol (31.1%) and carbamazepine (22.9%) were the causative drugs in more than half (54%) of the cases, followed by vancomycin (11.4%). Other than these three

drugs, antituberculosis agents, sulfasalazine, and valproic acid were shared as causative drugs by both the SJS/TEN and DRESS groups.

Clinical Features

All patients had various types of skin involvement. Among the 41 SJS/TEN patients, 37 (90%) suffered from skin detachment, and 4 had oral mucosal erosion only. Eighty-one percent of DRESS patients showed desquamation. Maculopapular eruptions were present in 67% of SJS/TEN patients and 85% of those with DRESS. Skin pain (89% for SJS/TEN vs. 54% for DRESS) and itching (94% for SJS/TEN vs. 83% for DRESS) were more prevalent in SJS/TEN compared with DRESS. The majority (88%) of SJS/TEN patients showed mucosal involvement, whereas 24% of DRESS patients had mucosal lesions. The oral cavity and lip were frequently involved in SJS/TEN and 2 (5%) SJS/TEN patients had ocular or genital lesions without oral cavity or lip involvement. However, the pattern of mucosal involvement was different in DRESS. In DRESS, 11 cases presented with mucosal involvement. There were 7 (63.6%) cases with oral cavity or lip involvement, 4 (36.4%) cases with ocular involvement and 4 (36.4%) cases with genital lesions. Four patients showed multiple mucosal involvement; 2 with oral cavity and ocular involvement, 1 with oral cavity and genital lesions, and 1 with oral cavity, ocular and genital involvement.

The percentage of patients with fever ($\geq 38^{\circ}\text{C}$) at presentation was similar for both disease entities (78% for SJS/

Table 2. Systemic manifestations in SJS/TEN and DRESS

	SJS/TEN (n = 41)	DRESS (n = 47)	p value
Fever, n	32 (78)	40 (85)	0.4
Lymphadenopathy, n	1 (3)	6 (13)	0.1
Anemia, n	34 (83)	41 (87)	0.6
Hemoglobin, g/dl	10.2 (6.9–12.4)	9.5 (5.6–14.5)	0.7
Leukocytosis, n	11 (28)	21 (46)	0.08
Initial leukocyte count, $\times 10^3/\mu\text{l}^{\text{a}}$	12.6 (10.6–18.6)	14.4 (10.6–73.2)	0.5
Initial neutrophil count, $\times 10^3/\mu\text{l}^{\text{a}}$	9.6 (5.2–10.8)	8.8 (4.4–32.9)	0.8
Initial lymphocyte count, $\times 10^3/\mu\text{l}^{\text{a}}$	1.3 (0.7–6.9)	1.7 (0.8–18.3)	0.3
Leukocytopenia, n	19 (48)	6 (13)	<0.001
Minimal leukocyte count, $\times 10^3/\mu\text{l}^{\text{b}}$	2.9 (0.4–4.0)	2.5 (0.6–3.3)	0.6
Minimal neutrophil count, $\times 10^3/\mu\text{l}^{\text{b}}$	1.2 (0.08–3.2)	1.6 (0.01–2.1)	0.7
Minimal lymphocyte count, $\times 10^3/\mu\text{l}^{\text{b}}$	0.4 (0.1–1.4)	0.5 (0.2–0.9)	1.0
Eosinophilia, n	4 (10)	33 (72)	<0.001
Maximal eosinophil count, $/\mu\text{l}^{\text{c}}$	1,057 (841–2,177)	1,948 (757–10,220)	0.1
Atypical lymphocytosis, n	8 (20)	15 (33)	0.2
Thrombocytopenia, n	10 (25)	7 (15)	0.3
Minimal platelet count, $\times 10^3/\mu\text{l}^{\text{d}}$	65 (19–77)	74 (30–98)	0.1
Renal involvement, n	4 (10)	8 (17)	0.3
ΔScr , mg/dl	1.7 (1.1–2.2)	1.4 (1.0–5.3)	1.0
Hepatic involvement, n (%)	19 (46)	35 (75)	0.007
Maximal ALT, IU/l ^e	207 (82–1,582)	234 (89–2,194)	0.8

Values are expressed as median with either range or percentage in parentheses. Scr = Serum creatinine; ALT = alanine transaminase; ΔScr = peak Scr – baseline Scr; fever = body temperature $\geq 38^\circ\text{C}$; leukocytosis = white blood cell count $>10,000$ at presentation; leukocytopenia = white blood cell count $<4,000$; eosinophilia = maximal eosinophil count $>700/\text{l}$; thrombocytopenia = platelet count $<100,000/\text{l}$; renal involvement = $\Delta\text{Scr} \geq 1.0$ mg/dl; hepatic involvement = ALT ≥ 80 IU/l.

^a Values of patients who had initial leukocytosis were used.

^b Values of patients who had leukocytopenia during hospitalization were used.

^c Values of patients who had eosinophilia during hospitalization were used.

^d Values of patients who had thrombocytopenia during hospitalization were used.

^e Values of patients who had hepatic involvement were used.

TEN and 85% for DRESS). Hematological abnormalities, such as anemia, leukocytosis, leukocytopenia, eosinophilia, atypical lymphocytosis and thrombocytopenia at presentation and during the hospital stay, were commonly found in both conditions. Leukocytosis ($\geq 10,000/\text{mm}^3$) at presentation was more common in DRESS, and leukocytopenia ($<4,000/\text{mm}^3$) during illness was more frequent in SJS/TEN. Eosinophilia was more common in DRESS than SJS/TEN, as expected (table 2). Renal function deterioration (17% for DRESS vs. 9.8% for SJS/TEN, $p = 0.3$) was more frequent in DRESS patients compared with SJS/TEN, but the difference was not significant. An abnormal serum level of alanine transaminase (74.5% for DRESS vs. 46.3% for SJS/TEN, $p = 0.007$) was significantly more frequent in DRESS.

SCORTEN

SCORTEN scores were assessed for 36 patients with available data to compare the expected mortality and the observed mortality. There were 13 patients with

SCORTEN score 0–1, 15 with score 2, 6 with score 3, 1 with score 4 and 1 with score 5. Among 4 patients who died, there were 2 with SCORTEN 3 (mortality 33%), 1 with SCORTEN 4 (mortality 100%) and 1 with SCORTEN 5 (mortality 100%). The expected mortality rate for the whole study population was 11.7% and the observed mortality rate was 10.8%.

Risk Factor Analysis

The extent of skin detachment was significantly related to mortality in SJS/TEN ($p = 0.02$). Other aspects of cutaneous involvement, such as the presence of skin detachment, mucosal erosion or maculopapular eruption, were not related to mortality in SJS/TEN. No laboratory abnormalities were related to increased mortality rate in either SJS/TEN or DRESS.

Prolonged hospitalization (longer than 3 weeks) and the risks for prolonged hospitalization were analyzed. Types or extents of mucocutaneous involvement and lab-

Fig. 3. Seasonal patterns of the development of SCARs. There was no significant seasonal pattern in the development of SCARs in this study. However, the accumulated number of SJS/TEN cases that developed in summer was relatively small, and that of DRESS in winter was also small.

oratory test abnormalities were not related to prolonged hospitalization. However, after excluding fatal cases and in-hospital cases, which could affect duration of admission, thrombocytopenia was significantly related to prolonged hospitalization for SJS/TEN (odds ratio, OR 6.6, 95% confidence interval, CI 1.1–39.3, $p = 0.05$) and leukocytosis at presentation for DRESS (OR 4.8, 95% CI 1.1–20.3, $p = 0.03$; for details see online suppl. table 1).

Seasonal Patterns

The seasonal pattern of occurrence of SCARs was analyzed. The accumulated number of SJS/TEN cases that developed in summer was relatively small, while more cases occurred in winter and spring (fig. 3). For DRESS, the largest number of patients developed this condition in spring, but there were no statistically significant seasonal differences ($p = 0.7$).

Treatments

For SJS/TEN, 19 patients were given only systemic corticosteroids, 11 only intravenous immunoglobulin (IVIG), and 9 systemic corticosteroids and IVIG. Two cases with SJS/TEN were treated conservatively. The dosage of IVIG was highly variable and ranged from 10 to 1,600 mg/kg/day (median 212.5 mg/kg/day). IVIG was used for a median of 4 days (range 1–8). The median dosage of systemic steroids was 40 mg methylprednisolone equivalent dose (range 7–375) and the median duration of systemic steroid treatment was 16.5 days (range 1–152). Among the 4 patients who died, 1 was given only system-

ic corticosteroid, 1 was treated with IVIG only, and 2 were treated with both systemic steroid and IVIG. Patients who received only supportive care were all SJS patients, and none died. There were no differences in mortality or hospitalization period according to treatment modality in SJS/TEN.

For DRESS, 40 patients were given systemic corticosteroids alone, and 1 patient was treated with both systemic corticosteroid and IVIG. Seven patients were treated conservatively. The maximal dosage of systemic steroid was median 44 mg prednisolone or equivalent dose (range 12–188), and the median duration of systemic steroid treatment was 44.5 days (range 3–1,295). There were no differences in the hospitalization period according to systemic steroid use in DRESS.

Discussion

The clinical characteristics of SCARs in a tertiary hospital in Korea were determined and compared between SJS/TEN and DRESS in this study. The study population consisted of 41 SJS/TEN patients and 47 DRESS patients over the 6-year study period. Mortality rates were 9.8% for SJS/TEN and 2.1% for DRESS.

Almost all the SJS/TEN patients acquired their disease within 6 weeks after initiation of causative agents. One patient developed SJS 64 days after initiation of allopurinol. In this case, the patient had underlying chronic renal failure and hepatitis B virus infection, and was prescribed

100 mg of allopurinol daily due to hyperuricemia. He also started metolazone and lamivudine within 3 months before initiation of eruption. However, metolazone and lamivudine were well tolerated when resumed after he recovered from SJS. DRESS started within the first 9 weeks of treatment except in 1 patient who had an eruption 128 days after starting allopurinol. She had HLA-B*5801, which is reported to be closely related to SCAR development in Korean and Han Chinese patients taking allopurinol [14, 15]. It generally took a longer exposure time to cause DRESS than SJS/TEN, and in the case of drugs with longer half-lives, such as allopurinol, it could take longer to develop SCAR than with other drugs [16–18].

In this study, most causative drugs, such as allopurinol, carbamazepine, sulfasalazine, valproic acid and vancomycin, commonly caused both SJS/TEN and DRESS. Allopurinol followed by carbamazepine was the most common culprit agent for SCARs in this study, as described in previous reports [16, 19]. Korea has a high prevalence of HLA-B*5801 in the general population [20] and subjects with the HLA-B*5801 allele were shown to have a greater risk of SCAR development when taking allopurinol [14]. The association between HLA-B*5801 and allopurinol hypersensitivity is strong in ethnic groups with a high frequency of HLA-B*5801 in the general population, such as the Han Chinese, Koreans and Thais [21]. Similarly, we recently reported the association between HLA-A*3101, which is one of the frequent HLA-A alleles in the general Korean population [20], and carbamazepine-induced SCARs in the Korean population [22]. In this study, SCARs due to vancomycin and antituberculosis agents were more prevalent than in previous reports from Korea [23, 24]. This may reflect the high prevalence of resistant strains of Gram-positive bacteria and tuberculosis. There were 3 cases of enalapril-induced SJS/TEN in this study, and a few cases of angiotensin-converting enzyme inhibitor-induced SJS/TEN have been reported in the literature [25]. However, the ALDEN scores of 2 of these 3 cases were 'unlikely', indicating that the accuracy of inference of causality might be doubtful. Despite similarities in causative agents and genetic susceptibility, SJS/TEN and DRESS showed clinically different manifestations. However, it is still difficult to classify these phenotypes clearly, and the classification of SCARs remains controversial [3].

T cells were considered to play key roles in drug hypersensitivity reactions, and the subtypes of T cells that participate in hypersensitivity reactions were thought to differ according to the type of reaction [5]. Cytotoxic CD8+ T cells in SJS/TEN and CD4+ T cells in DRESS are con-

sidered the key players in these hypersensitivity reactions. However, there are still controversies regarding the pathogenesis and major cell types involved in SCARs.

Several lines of evidence suggest that drug-specific T cells may play an important role in immune-mediated delayed reactions to drugs, such as SCARs. For SJS/TEN, the bullae contain many cytotoxic CD8+ T cells, which are thought to play a key role in the massive cell death of keratinocytes, and FasL and granulysin are thought to be key molecules [26–28]. In the circulation of DRESS patients, there are many activated drug-specific T cells, which are mostly CD4+ T cells with occasional CD8+ T cells [29]. Moreover, in a recent study, CD8+ T cells rather than CD4+ T cells were found in the peripheral blood, skin tissues and lung tissues of DRESS patients [30]. These findings suggest that SJS/TEN and DRESS could be similar in the pathogenesis.

The distinct patterns of cutaneous involvement of SJS/TEN and DRESS may result from different immune cell populations participating in the immune responses. However, patients with SJS/TEN may have maculopapular eruption at presentation similar to those with DRESS. In this study, we also found that 67% of SJS/TEN patients initially presented with maculopapular eruption. Patients with SJS/TEN suffered from skin detachment and mucosal involvement, but a quarter of DRESS patients also experienced mucosal involvement, with features different from those of SJS/TEN. Mucosal involvement in DRESS has been described in previous studies since the term 'DRESS' was coined [2, 31]. SJS/TEN often has accompanying internal organ involvement, such as hepatic and renal involvement, which is typically observed in DRESS [1]. Although internal organ involvement presents more frequently in DRESS, a considerable number of SJS/TEN patients also show hepatic or renal abnormalities. Other investigators have reported that almost all SJS/TEN patients presented with hematological abnormalities [32], and we found that 100% of patients in the present study had at least one hematological abnormality. In particular, thrombocytopenia was observed in a quarter of SJS/TEN patients. Eosinophilia and atypical lymphocytosis are characteristic features and are included in the diagnostic criteria of DRESS. However, a considerable number of SJS/TEN patients also showed eosinophilia and atypical lymphocytosis in the present study. Therefore, problems in diagnosis can arise in such cases with mixed clinical features [1]. At present, it is not easy to differentiate clearly between the two disease entities, and further studies are needed to understand the pathomechanisms of these two conditions.

Although SCARs are very serious medical conditions, prognostic markers are not well established. A few studies have been conducted to evaluate the risk factors for mortality in SJS/TEN. SCORTEN is the best-known scoring system to calculate the probability of mortality in SJS/TEN. It includes seven clinical variables: age, extent of involved body surface area, heart rate, presence of malignancy, and serum urea, glucose and bicarbonate levels [12]. Histology of the involved skin, bronchial epithelial necrosis, hypernatremia and serum lactate dehydrogenase have been suggested to be markers of disease severity [6–8, 33–35]. Other than SCORTEN, thrombocytopenia has been suggested to be a prognostic factor in SJS/TEN. However, the results have been inconsistent [36, 37]. In the present study, thrombocytopenia seemed to be marginally related to prolonged hospitalization after adjusting for covariates in SJS/TEN patients (OR 5.1, 95% CI 0.8–31.8, $p = 0.076$). For DRESS, there have been few reports on prognostic factors, such as high eosinophilia, multiple underlying diseases and pancytopenia [16, 38]. Recently, Wei et al. [9] reported that prognostic factors for mortality in DRESS are tachycardia, leukocytosis, tachypnea, coagulopathy, gastrointestinal bleeding and systemic inflammatory response syndrome. In this study leukocytosis at presentation was a prognostic factor for prolonged hospitalization for DRESS patients, and was largely attributed to neutrophilia (data not shown), which could imply elevated inflammatory activities at presentation (i.e. more severe disease).

There was a previous report on the seasonal pattern of development of SJS/TEN associated with sulfamethoxazole-trimethoprim [39]. However, the authors found no seasonal association with SJS/TEN occurrence in a larger population from the SCAR study and EuroSCAR [40]. Although we found no significant differences in the development of SJS/TEN in our cases, SJS/TEN seemed to occur less frequently in summer. Further studies are required to investigate this issue because it may yield insight

into the disease pathomechanism. We failed to show the clinical efficacy of IVIG and systemic steroids in the treatment of SJS/TEN because of the individual heterogeneous conditions and the limited number of patients included in the study population.

There were several limitations in this study. We selected our cases using an electronic medical record and our own selection protocol, which was not previously validated. Thus, some cases may have been inappropriately included or excluded. For example, there were only 6 SJS/TEN cases with skin biopsies. Although the results of these 6 biopsies were compatible with SJS/TEN, 35 cases were not confirmed by pathologic findings. Thus, there were possibilities for some diseases that could mimic SJS/TEN to be included. There were also possibilities for misinference of the causative agents, as we have shown by calculating ALDEN scores. Recently there was a report that preexisting renal or hepatic failure were negative prognostic factors [41]. However, we could not assess the effects of preexisting renal or hepatic failure on the prognosis because of the limited numbers of patients. As this was a retrospective study, the cohort included some cases with missing values. In addition, as with other small series dealing with SCARs, there was a limitation in the number of study patients.

In conclusion, risk factors for prolonged hospitalization were thrombocytopenia in SJS/TEN and leukocytosis in DRESS. SJS/TEN and DRESS showed some clinical and laboratory similarities, and the relationship between the two disease entities should be investigated further.

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