Clinical characteristics of drug-induced Stevens-Johnson syndrome and toxic epidermal necrolysis: A single-center study

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ABSTRACT

Background: Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) are severe adverse cutaneous reactions, most commonly triggered by medications, characterized by extensive necrosis and detachment of the epidermis.

Objective: We investigated the differences in clinical characteristics of drug-induced SJS/TEN depending on the type of drug in a single center.

Methods: The relevance of sex, age, culprit drugs, clinical features, courses, treatment options, and follow-up results were retrospectively evaluated in patients diagnosed with drug-induced SJS/TEN at Pusan National University Hospital between 2008 and 2019.

Results: Ninety-two patients with a mean age of 58.7 ± 20.2 years (range, 10–93 years) were included in the study. Those aged 60–80 years accounted for the largest number of patients (42.4%). Patients with drug-induced SJS/TEN comprised 40 women (43.5%) and 52 men (56.5%). We categorized drug-induced SJS/TEN cases by culprit drugs into 6 groups: antibiotics, allopurinol, antiepileptic (AED), nonsteroidal anti-inflammatory drugs (NSAIDs), acetaminophen, and other drugs. The rate of NSAID-induced disease significantly increased from SJS to TEN (p = 0.016). Among the patients in the NSAID group, the proportion of TEN (40%) was higher than that in the other groups (p = 0.021). The mean body surface area was significantly lower in the AED group than in the non-AED groups (7.1 ± 9.8 vs. 23.1 ± 27.3, p = 0.020) and higher in the NSAID group than in the non-NSAID groups (47.5 ± 39.5 vs. 15.7 ± 20.0, p = 0.010).

Conclusion: This study showed that the clinical characteristics of each causative drug group may be different in drug-induced SJS/TEN. Our findings may help clinicians better understand drug-induced SJS/TEN.

Keywords: Adults; Child; Drug; Stevens-Johnson syndrome; Toxic epidermal necrolysis

INTRODUCTION

Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) are severe adverse cutaneous reactions (SCAR), most commonly triggered by medications, characterized by
extensive necrosis and detachment of the epidermis. SJS involves a characteristic macular rash with painful blistering and bullous lesions, fever, purulent conjunctivitis, and stomatitis [1]. TEN, also known as Lyell’s syndrome, is a more serious and potentially life-threatening condition [2], with SJS having a mortality rate of 5%–10%, while TEN has a mortality rate of up to 30%–40% [3, 4]. The criteria of Bastuji-Garin et al. [5] were used in the diagnosis of SJS/TEN in which patients were classified into 3 categories based on the degrees of skin detachment; SJS involved less than 10% of total body surface area (TBSA), whereas SJS/TEN overlap involved 10%–30% TBSA, and TEN involved more than 30% TBSA [6]. Annual incidence rates of SJS range from 1 to 6 cases per million people per year, and those of TEN range from 0.4 to 1.45 cases per million people per year [7].

The etiology and pathologic mechanisms that induce skin damage in SJS/TEN are not completely understood. Early studies of the immunophenotype of lymphocytes detected in the blister fluid of SJS/TEN lesions suggested a cell-mediated cytotoxic reaction against keratinocytes leading to massive apoptosis [8]. Subsequent studies demonstrated that cytotoxic T cells are drug-specific, human leukocyte antigen class I restricted, and directed against the native form of the drug rather than against a reactive metabolite [9]. Drugs can stimulate the immune system by directly binding to major histocompatibility complex class I and T-cell receptors. This results in the clonal expansion of a population of drug-specific cytotoxic T cells that kill keratinocytes directly and indirectly through the recruitment of other cells that release soluble death mediators, including granulysin [10].

Many studies have shown that the causative agents as a result of a hypersensitivity reaction to various types of drugs, such as anticonvulsants, sulfonamides, other antibiotics, nonsteroidal anti-inflammatory drugs (NSAIDs), antifungals, antimalarials, and allopurinol [4, 11]. The syndrome usually begins 4–14 days after the initiation of drug therapy but may not be visible for 3–6 weeks after ingestion [6]. However, to date, there is little information about the differences in clinical symptoms of drug-induced SJS/TEN depending on the type of drug. Therefore, we investigated the differences in clinical characteristics of drug-induced SJS/TEN depending on the type of drug used.

**MATERIALS AND METHODS**

We analyzed the electronic medical records of all patients diagnosed with drug-induced SJS/TEN at Pusan National University Hospital, Busan, Republic of Korea, between January 1, 2008, and December 31, 2020. Their medical records were reviewed to include only patients who met the drug-induced SJS/TEN diagnostic criteria. Clinical symptoms for SJS should include acute conditions characterized by mucous membrane erosions and skin lesions (described as macules, atypical target-like lesions, bulla, or erosions) within in this spectrum of epidermal necrolysis [12]. When we analyzed causative drugs, patients who took 2 or more drugs-selected the drug as a newly added or using Naranjo scale based on medical records (Table 1) [13]. This study protocol was approved by the Institutional Review Board of Pusan National University Hospital (PNUH IRB 2101-017-099).

Detailed medical information, including data on demographics, hospitalization, timing from disease onset to admission, medication histories, latent period, presence of mucous membrane involvement, physical examination, medical comorbidities, laboratory results, associated complications, clinical course, treatments, duration of hospital stay, outcome,
and observed mortalities, were extracted from the medical records. All patients with photographs and BSA were reviewed by a dermatologist. A severity-of-illness scoring system for TEN (SCORTEN) prognosis was used to evaluate the efficacy of treatments and compare the predicted mortality rate. It consists of 7 clinical parameters within the first 24 hours of admission; (1) age ≥ 40 years, (2) skin detachment ≥ 10% of total BSA, (3) heart rate ≥ 120 beats/min, (4) serum blood urea nitrogen > 28 mg/dL, (5) serum bicarbonate < 20 mEq/L, (6) serum glucose > 252 mg/dL, and (7) malignancy present [14]. Each variable had an equal weight in the score.

Statistical analyses were performed using IBM SPSS Statistics ver. 20.0 (IBM Co., Armonk, NY, USA). The demographic data are presented as the mean ± standard deviation. Categorical variables were presented as frequencies with percentages. The clinical features of SJS, SJS/TEN overlap, and TEN patients were analyzed by linear-by-linear association or Kruskal-Wallis test. Fisher exact test was applied to analyze categorical data, and the Mann-Whitney test was used for continuous variables. Statistical significance was set at \( p < 0.05 \).

**RESULTS**

As shown in Table 2, 92 patients with drug-induced SJS/TEN were included in this study. Mean age at diagnosis was 58.7 ± 20.2 years (from 10 months to 93 years). When classified by the age of the patients at diagnosis, the most common patients were 60–80 years old (42.4%). Patients with drug-induced SJS/TEN comprised 40 women (43.5%) and 52 men (56.5%). Of all cases, 68.5% (n = 63) were diagnosed with SJS, 14.1% (n = 13) were diagnosed with SJS/TEN overlap, and 17.4% (n = 16) were diagnosed with TEN. The mean BSA of the skin at diagnosis was 19.9 ± 25.3. None of the patients had previous SCARs.

The latent period between causative drug intake and the onset of the manifestations in all patients ranged from 2 to 50 days, with a mean of 16.3 ± 9.7 days. Seventy-four patients (80.4%) were administered a single drug, while 18 (19.6%) received one suspected drug together with another medication unrelated to SJS/TEN. Sixty-nine patients (75%) ingested the medication(s) orally, 22 patients (23.9%) were administered the drug(s) intravenously (IV) or subcutaneous, and 1 patient (1.1%) used the medicine as an eye drop.

Eighty-eight patients (95.7%) were admitted to the hospital, only 4 patients (4.3%) were treated at the outpatient clinic. Of all the patients examined, 70 (76.1%) received systemic steroids or intravenous immunoglobulin (IVIG), and 15 (16.3%) received both systemic...
steroids and IVIG. Seven patients (7.6%) received conservative treatment only. The duration of treatment for all patients ranged from 5 to 40 days (mean, 17.9 ± 9.9 days). Most patients fully recovered (91.3%).

The culprit drugs for all the patients were identified (Table 3). Antibiotics were the most common causative drugs in 30.4% (n = 28) of drug-induced SJS/TEN patients, and amoxicillin/clavulanate was the most common drug among them. Allopurinol was the most common single drug in all patients (21.7%). Antiepileptics were the causative agent in 17 patients (18.5%). Among the antiepileptics, carbamazepine was the most common (70.6%). NSAIDs were the causative agents in 15 patients (16.3%) with piroxicam, ibuprofen, loxoprofen, and meloxicam (46.7%) was the most commonly listed specific NSAID triggers. Acetaminophen was induced acetaminophen. Other culprit drugs included herbal medicine, acetazolamide, methazolamide, potassium chloride, oxiracetam, and sulfasalazine.

We compared patients with SJS/TEN types (Table 4). The mean age of diagnosis was 57.9 ± 21.3 years in SJS, 63.8 ± 19.2 years in SJS/TEN overlap, and 57.6 ± 17.7 years in TEN. Females were predominant in SJS/TEN overlap (53.8%), and males were predominant in SJS (57.1%) and TEN (62.5%). The rate of NSAID-induced disease significantly increased from SJS to TEN (p = 0.016). The rate of taking 2 or more drugs was higher in patients with SJS/TEN overlap.
and TEN than in patients with SJS (p = 0.015). The mortality rates tended to increase from SJS to TEN, but the difference was not statistically significant. (p = 0.142)

In addition, we categorized drug-induced SJS/TEN cases by culprit drugs into 6 groups: antibiotics, allopurinol, antiepileptic drugs (AED) group, NSAIDs, acetaminophen, and other causative drugs. We compared the group who took the drug and the group that did not, depending on the causative class of the drug. The clinical characteristics of each drug are presented in Table 5. The mean age at diagnosis was higher in the allopurinol group (66.5 ± 15.3 years). Only 2 patients in the acetaminophen group were younger than the other groups (37.5 ± 9.2 years). Women were more frequently affected than men in the antibiotics (53.6%) and NSAID groups (53.3%). However, the difference was not statistically significant.

Among the patients in the NSAID group, the proportion of TEN patients was higher than that in the other groups (40%, p = 0.021). The mean BSA at diagnosis was 7.1 ± 9.8 in the AED group, which was significantly lower than that in the non-AED group (p = 0.020). In the NSAID group, BSA was 47.5 ± 39.5, which was significantly higher than that in the non-NSAID group (p = 0.010). However, there was no statistical difference between the groups when comparing SCOREN (p = 0.388) and mortality (p = 0.345).

The longest latent period was 21.6 ± 10.4 days in the allopurinol group, followed 16.4 ± 9.3 days in the AED group. The shortest latent period was for the acetaminophen group. Allopurinol and the AED groups were administered drugs orally, and 60.8% of the antibiotics group (more than half) were administered IV. As a treatment option, 70% of all patients were treated with steroids or IVIG alone. Comparing each drug group, 21.4% of the antibiotics group received a combination of steroids and IVIG, and 15% of the allopurinol group received the combination therapy. Only one patient in the NSAID group received a combination

### Table 3. Kind, number of suspected drugs as the etiology (n=92)

| Etiology         | No. (%)   |
|------------------|-----------|
| Antibiotics      | 28 (30.4) |
| - Beta-lactam antibiotics | 20        |
| - Sulfonamides   | 5         |
| - Fluoroquinolines | 3         |
| Allopurinol      | 20 (21.7) |
| Antiepileptics   | 17 (18.5) |
| - Carbamazepine  | 12        |
| - Lamotrigine    | 2         |
| - Gabapentin     | 1         |
| - Levetiracetam  | 1         |
| - Oxcarbazepine  | 1         |
| NSAIDs           | 15 (16.3) |
| - Meloxicam      | 7         |
| - Piroxicam      | 3         |
| - Ibuprofen      | 3         |
| - Loxoprofen     | 2         |
| Acetaminophen    | 2 (2.2)   |
| Other drugs      | 10 (10.9) |
| - Herbal medicine | 4         |
| - Acetazolamide  | 2         |
| - Methazolamide  | 1         |
| - Potassium chloride | 1       |
| - Oxiracetam     | 1         |
| - Sulfasalazine  | 1         |

NSAIDs, nonsteroidal anti-inflammatory drugs.
The duration of treatment was the longest in the NSAIDs group (20.4 ± 10.7 days) and the shortest in the AED group (15.2 ± 9.8 days). Most of the patients who received treatment recovered. Eight patients died, of which 5 were in the antibiotic group and 3 in the allopurinol group.

Table 4. Clinical manifestations according to Stevens-Johnson syndrome and toxic epidermal necrolysis type

| Characteristic | Total (n=92) | SJS (n=63) | SJS/TEN overlap (n=13) | TEN (n=16) | p value |
|----------------|-------------|------------|------------------------|------------|---------|
| Age (yr)       | 58.7±20.2   | 57.9±21.3  | 63.8±19.2              | 57.6±17.7  | 0.581   |
| Female sex (%) | 43.5        | 42.9       | 53.8                   | 37.5       | 0.878   |
| Latent period (day) | 16.3±9.7     | 16.9±10.3  | 18.0±9.1               | 12.2±8.1   | 0.190   |
| Culprit drug   |             |            |                        |            |         |
| Antibiotics    | 28          | 16         | 6                      | 6          | 0.210   |
| Allopurinol    | 20          | 16         | 2                      | 2          | 0.219   |
| Antiepileptics | 17          | 15         | 1                      | 1          | 0.066   |
| NSAIDs         | 15          | 7          | 2                      | 6          | 0.016   |
| Acetaminophen  | 2           | 1          | 1                      | 0          | 0.984   |
| Other drugs    | 10          | 8          | 1                      | 1          | 0.111   |
| Medications number |             |            |                        |            | 0.015*  |
| ≤2             | 74 (80.4)   | 57 (90.5)  | 5 (38.5)                | 12 (75)    |         |
| >2             | 18 (19.6)   | 6 (9.5)    | 8 (61.5)                | 4 (25)     |         |
| Route of administration |           |            |                        |            | 0.142   |
| Oral           | 69 (75.0)   | 47 (74.6)  | 10 (76.9)               | 12 (75)    | 0.938   |
| IV or SC       | 22 (23.9)   | 15 (23.8)  | 3 (23.1)                | 4 (25)     | 0.940   |
| Eyedrop        | 1 (1.1)     | 1 (1.6)    | 0 (0)                  | 0 (0)      | 0.527   |
| Duration of treatment (day) | 17.9±9.9  | 16.5±9.6   | 20.4±10.5              | 21.4±10.0  | 0.127   |
| Clinical course |           |            |                        |            |         |
| Recovery       | 84 (91.3)   | 59 (93.7)  | 12 (92.3)               | 13 (81.3)  | 0.273   |
| Death          | 8 (8.7)     | 4 (6.3)    | 1 (7.7)                | 3 (18.7)   |         |

Values are presented mean ± standard deviation or number (%).
SJS, Stevens-Johnson syndrome; TEN, Toxic epidermal necrolysis; NSAIDs, nonsteroidal anti-inflammatory drugs; IV, intravenous; SC, subcutaneous.
*p < 0.05 was considered statistically significant.

Table 5. Clinical characteristics in Stevens-Johnson syndrome and toxic epidermal necrolysis according to the causative drugs

| Characteristic | Antibiotics (n=28) | Allopurinol (n=20) | AED (n=17) | NSAIDs (n=15) | Acetaminophen (n=2) | Others (n=10) |
|----------------|--------------------|--------------------|------------|---------------|--------------------|---------------|
| Age (yr)       | 60.5±18.8          | 66.5±15.3          | 55.9±22.7  | 55.8±23.0     | 37.5±9.2          | 51.6±23.3     |
| Female sex (%) | 43.5               | 42.9               | 53.8       | 37.5          | 30 (100)          | 40.0          |
| Type of SJS/TEN |                    |                    |            |               |                    |               |
| SJS            | 16 (57.2)          | 16 (80.0)          | 15 (88.2)  | 7 (46.7)      | 1 (50.0)          | 8 (80.0)      |
| SJS/TEN overlap | 6 (21.4)           | 2 (10.0)           | 1 (5.9)    | 2 (13.3)      | 1 (50.0)          | 1 (10.0)      |
| TEN            | 6 (21.4)           | 2 (10.0)           | 1 (5.9)    | 6 (40.0)*     | 0 (0)             | 1 (10.0)      |
| Involved BSA   | 24.9±23.6          | 11.3±15.2          | 7.1±9.8*   | 47.5±39.5*    | 10±7.1            | 20.8±28.0     |
| SCORTEN        | 2.1±1.1            | 1.9±1.0            | 1.2±1.0    | 1.9±1.2       | 0.5±1.7           | 1.3±0.8       |
| Latent period (day) | 13.1±9.4         | 21.6±10.4          | 16.4±9.3   | 14.9±7.7      | 5±1.4             | 18.5±11.2     |
| Route of administration |                |                    |            |               |                    |               |
| Oral           | 11 (39.2)          | 20 (100)           | 17 (100)   | 11 (73.3)     | 2 (100)           | 8 (80.0)      |
| IV or SC       | 17 (60.8)          | 0 (0)              | 0 (0)      | 4 (26.7)      | 0 (0)             | 1 (10.0)      |
| Eyedrop        | 0 (0)              | 0 (0)              | 0 (0)      | 0 (0)         | 0 (0)             | 1 (10.0)      |
| Treatment options |                |                    |            |               |                    |               |
| Supportive     | 4 (14.3)           | 1 (5.0)            | 1 (5.9)    | 1 (6.7)       | 0 (0)             | 0 (0)         |
| Corticosteroid or IVIG | 18 (64.3)        | 16 (80.0)          | 15 (88.2)  | 13 (86.6)     | 2 (100)          | 6 (60.0)      |
| Corticosteroid and IVIG | 6 (21.4)         | 3 (15.0)           | 1 (5.9)    | 1 (6.7)       | 0 (0)             | 4 (40.0)      |
| Duration of treatment (day) | 17.7±10.5       | 18.2±9.1           | 15.2±9.8   | 20.4±10.7     | 19.5±7.8         | 18.4±10.4     |
| Clinical course |                |                    |            |               |                    |               |
| Recovery       | 23 (82.1)          | 17 (75.0)          | 17 (100)   | 15 (100)      | 2 (100)           | 10 (100)      |
| Death          | 5 (17.9)           | 3 (15.0)           | 0 (0)      | 0 (0)         | 0 (0)             | 0 (0)         |

Values are presented mean ± standard deviation or number (%).
SJS, Stevens-Johnson syndrome; TEN, Toxic epidermal necrolysis; AED, antiepileptic drug; NSAIDs, nonsteroidal anti-inflammatory drugs; IV, intravenous; SC, subcutaneous; SCORTEN, a severity-of-illness score for toxic epidermal necrolysis; IV, intravenous; SC, subcutaneous; IVIG, intravenous immunoglobulin.
*p < 0.05 was considered statistically significant.
DISCUSSION

In this study, we present the clinical characteristics of drug-induced SJS/TEN. When the clinical characteristics of drug-induced SJS/TEN were compared, BSA and the ratio of TEN were significantly higher in the NSAID group. In addition, the BSA was significantly lower in the AED group. Antibiotics and allopurinol are the drugs that cause death. To our knowledge, there have been few studies comparing clinical manifestation differences between drug groups in drug-induced SJS/TEN. This study provides valuable data to show that each drug may have different characteristics in drug-induced SJS/TEN.

Zhang et al. [15] showed that the female predominance in drug-induced SJS/TEN, and other published data showed that females are most commonly affected, represented by a female-male ratio of 3:2 [16]. However, the demographic data of our study represented the male predominance of drug-induced SJS/TEN. Similar to our study, in other previous studies, there were more drug-induced SJS/TEN in men than in women [14, 17, 18]. The incidence of drug-induced SJS/TEN increases with increasing age, as does the use of drugs with ageing [19]. The mean age of patients reported is between the ages of 46 and 63, respectively [20]. In our study, the mean age of SJS/TEN patients was 58.7 ± 20.2 years and the most prevalent age was identified as 60–80 years old.

Antibiotics, as in the previous studies, were the most common drugs implicated in our study [21]. Penicillin and sulfonamides were the most common drugs causing SJS/TEN in several previously published reports [21]. Similarly, in our study, amoxicillin/clavulanate accounted for the largest proportion of antibiotics. Allopurinol was the single drug found to cause the second highest proportion of SJS/TEN cases in this study. Allopurinol is usually considered a safe drug, and due to its frequent administration, increased risk for SJS/TEN possible [16]. Among the patients who died in this study, 5 (62.5%) used antibiotics and 3 (37.5%) used allopurinol. There were no statistical differences; this tendency may have been influenced by the characteristics of each drug and the various or severe underlying diseases of the patients. Therefore, the selection and prescription of these drugs should be carefully considered.

In a previous study, nearly 93% of patients had drug-induced SJS/TEN attributable to only one drug [22]. In our study, 80.4% of all patients were induced by a single causative medication. In addition, we found that the rate of taking more than 2 or more drugs increased from SJS to TEN. In another study conducted by Oh et al. [23], of 92 Korean pediatric patients with SCAR, in SJS, the case induced by a single drug predominated, whereas in TEN, 50% of them were prescribed 2 or more drugs, and the number of medications increased from SJS to TEN.

Several previously published reports have described the clinical characteristics, causative agents, and risk factors of AED-induced SJS/TEN and DRESS (drug reaction with eosinophilia and systemic symptoms) [24]. Although some previous studies showed BSA in AED-induced SJS/TEN patients [25, 26], this value has not been accurately presented. Therefore, a comparison with our study is not possible. In addition, there was no comparative analysis between AED-induced SJS/TEN and the non-AED group.

Although NSAIDs have been associated with SJS and TEN in the literature, most reports have been small series or individual case reports [27, 28]. In our study, when comparing the NSAIDs-induced SJS/TEN group and the non-NSAIDs group, there was no difference of the age, male predominance, incubation period, treatment options, and duration of treatment.
However, patients with NSAID-induced SJS/TEN were more frequent in TEN than in SJS and higher in BSA, but did not affect SCORTEN or mortality. Further studies are required with regard to the limited number of drug-induced SJS/TEN patients in our study.

The association between acetaminophen and SJS/TEN has been debated by experts, and few cases have been reported [29]. In this study, only 2 cases of acetaminophen-induced SJS/TEN were identified. The patients had no findings suggesting other culprit drugs or infections. Although not statistically significant, the latent period was shorter in patients taking acetaminophen than in the other groups.

Our study had several limitations. The present study was a retrospective study in which only medical records were analyzed from a single center specialized in treating allergies, and the number of samples was small. Because it was based on medical records, some data may be incomplete or missing. Thus, a well-designed large sample study is needed to provide a basis for future research.

In conclusion, this study showed that the clinical characteristics of each causative drug group may be different in drug-induced SJS/TEN. Our findings may help clinicians better understand drug-induced SJS/TEN.

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