

Original Article

Searching for the Culprit Drugs for Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis from a Nationwide Claim Database in Korea

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What is already known about this topic? Some drugs cause Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) more common than other drugs. However, common causative drugs of these diseases can be different depending on ethnicity.

What does this article add to our knowledge? The common causes of SJS and TEN were different depending on ethnicity, and the method used in this study could be helpful in estimating the common cause of SJS and TEN in a specific population.

How does this study impact current management guidelines? To identify the cause of SJS and TEN, it seems necessary to consider the common causative drugs of these diseases in a specific population, which can be estimated by analyzing a large database.

BACKGROUND: Ethnic differences exist in relation to culprit drugs for Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN). We wanted to determine culprit drugs for SJS and TEN in Korean population.

OBJECTIVE: To evaluate culprit drugs for SJS and TEN by applying an algorithm for assessment of drug causality for epidermal necrolysis (ALDEN) in a nationwide administrative database.

METHODS: We used the claims database, which included claims data for the entire South Korean population. A retrospective cohort study was conducted by collecting subjects who were first diagnosed with SJS and TEN in 2011. All drugs prescribed to the subjects were reviewed and scored according to the ALDEN score. Drugs with an ALDEN score ≥ 2 were considered culprit drugs.

RESULTS: A total of 187 subjects were included in the culprit drug analysis; 33 very probable, 101 probable, and 57 possible culprit drugs were identified for SJS and TEN according to the ALDEN score. The most frequently suspected culprit drug was allopurinol

(19 cases), followed by carbamazepine (17 cases), lamotrigine (13 cases), amoxicillin (9 cases), and dorzolamide (9 cases). Most cases (78.8%, 52 of 66) associated with the use of allopurinol, carbamazepine, lamotrigine, dorzolamide, and methazolamide occurred between 13 and 44 days after initiating the drug.

CONCLUSION: We applied the ALDEN score to the claims database to identify possible culprit drugs for SJS and TEN in South Korea. This approach could shed light on research and policymaking for drug adverse reactions. © 2019 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2019;■:■-■)

Key words: Stevens-Johnson syndrome; Pharmaceutical preparations; Causality; Logic; Health care administrative claims

Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) are rare but potentially fatal diseases. The most important risk factor for the development of SJS and TEN is exposure to a specific drug. It is well recognized from previous

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Abbreviations used

ALDEN- Algorithm for assessment of drug causality for epidermal necrolysis
 ATC- Anatomical Therapeutic Chemical
 CAI- Carbonic anhydrase inhibitor
 DDD- Defined daily dose
 HIRA- Health Insurance Review and Assessment Service
 HLA- Human leukocyte antigen
 ICD-10- International Classification of Diseases, 10th revision
 ICD-10-CM- International Classification of Diseases, 10th revision, clinical modification
 NSAID- Nonsteroidal anti-inflammatory drug
 SJS- Stevens-Johnson syndrome
 TEN- Toxic epidermal necrolysis
 TMP-SMX- Trimethoprim-sulfamethoxazole

case-control studies that some drugs cause SJS and TEN more often than other drugs.¹ The SCAR study reported that high relative risks for the development of SJS and TEN were observed for the antibiotic sulfonamide, aromatic anticonvulsants, oxicam nonsteroidal anti-inflammatory drugs (NSAIDs), allopurinol, chlormezanone, aminopenicillins, cephalosporins, fluoroquinolones, and cycline antibiotics. In the EuroSCAR study, which was published 13 years after the initial SCAR study, exposure to nevirapine and lamotrigine was strongly associated with the development of SJS and TEN.² Exposure to sertraline, pantoprazole, and tramadol was less strongly associated. They also confirmed the association between the development of SJS and TEN and the antibiotic sulfonamide, allopurinol, aromatic anticonvulsants, and oxicam NSAIDs. Furthermore, the distribution of the number of days between initiating the drug and the onset of the adverse reaction (time latency) was aggregated between 4 and 28 days for strongly associated drugs.² Thus, the shape of the distribution curve resembled that of an epidemiological curve for a point-source outbreak.³ Subsequently, the RegiSCAR group used 2 case-control studies and their own registry to construct an algorithm for assessment of drug causality for epidermal necrolysis (ALDEN).⁴ The ALDEN score is recognized as one of the most reliable tools for identifying culprit drugs for SJS and TEN.⁵

The number of strongly associated drugs may increase as new drugs appear on the market, as shown by the 2 case-control studies described above. The SJS and TEN culprit drugs may also depend on regional prescription patterns and ethnicity, as shown by a human leukocyte antigen (HLA) study.⁶ For example, HLA-B*15:02 is a risk allele for carbamazepine-induced SJS and TEN in Chinese ethnic groups. However, carbamazepine-induced SJS and TEN are not associated with HLA-B*1502 in either Koreans or Japanese.⁶ Thus, every nation and ethnicity needs to identify their own drugs of risk for SJS and TEN. However, it is very difficult to collect specific ethnicity data on SJS and TEN because of the rarity of the diseases. In this study, we applied a new method to estimate culprit drugs for SJS and TEN in the Korean population using nationwide claims data and the ALDEN score.

METHODS**Data sources and case selection**

We used the Health Insurance Review and Assessment Service (HIRA) claims database, which includes the medical records of all

Korean people, as described previously.⁷ The HIRA is an independent Korean governmental agency responsible for evaluating medical claims data from all health care organizations and medical facilities. It provides data on individuals' sex, age, type of insurance, date(s) of visit, primary and additional diagnostic codes, date(s) of prescription, drug names and dosages, number(s) of prescription days, and dates of hospitalization and discharge (if hospitalized). The HIRA gathered 1.3 billion medical claims from the Korean people in 2011.

Patients who were hospitalized with the primary diagnostic codes of L511 (SJS) or L512 (TEN) in the International Classification of Diseases (ICD), 10th revision in 2011 were selected. As only 5 years of data could be attained from HIRA, cases from 2011, which was the mid-point of the 2009-2013 study period, were used. It was considered reasonable to allocate a set period of time (in this case, at least 2 years each) to examine the effects of exposure to the same drugs for both the prechallenge and rechallenge scenarios. When the primary diagnostic code for a subject was changed from SJS or TEN to other differential diagnoses for bullous skin diseases, such as Staphylococcal scalded skin syndrome (L00) or a bullous disorder (L10-L14), then the subject was excluded. We considered subjects whose initial diagnoses of SJS were ultimately changed to TEN to be TEN cases. Subjects who were not hospitalized or discharged within 5 days after hospitalization were also excluded because 5 days is the shortest length of hospitalization from a previous study.⁸ However, if a subject died within 5 days of hospitalization, they were included as a case. When a subject was not exposed to a drug with an ALDEN score of ≥ 2 , the subject was considered as not having drug-induced SJS or TEN (Figure 1).

The Anatomical Therapeutic Chemical (ATC) classification system was used to classify the suspected culprit drugs. The fifth level of each substance was used as the fifth level of the ATC code, which describes substances with the same anatomical distribution, therapeutic and pharmacological effects, and chemical structures.

Identifying the culprit drugs

To identify the culprit drugs, an algorithm for assessing drug causality in ALDEN was applied.⁴ ALDEN is an algorithm proposed by the RegiSCAR study group to identify culprit drugs for SJS and TEN. Detailed information on ALDEN has been provided previously.⁴ In short, the following 6 criteria were scored for each drug, and drug causality was determined by the sum of the scores:

- (1) Time latency
- (2) Drug present in the body on the day of onset of the reaction (index day)
- (3) Prechallenge/rechallenge
- (4) Dechallenge
- (5) Type of drug (notoriety)
- (6) Other cause.

The final ALDEN score was between -12 and 10. When a drug had an ALDEN score of ≥ 6 , the drug was classified as a very probable cause of SJS and TEN. If a drug had an ALDEN score of 4 or 5, it was a probable cause for SJS and TEN. In the same way, a drug with an ALDEN score of 2 or 3 was classified as a possible cause, that with a score of 0 or 1 was an unlikely cause, and that with a score of less than 0 was a very unlikely cause.

We made a few assumptions in applying the ALDEN score to the HIRA database. The most important first step in applying the ALDEN score is to identify the index day. The index days were divided into the definite index day and the probable index day.⁹ The definite index day was when the first objective signs appeared, and

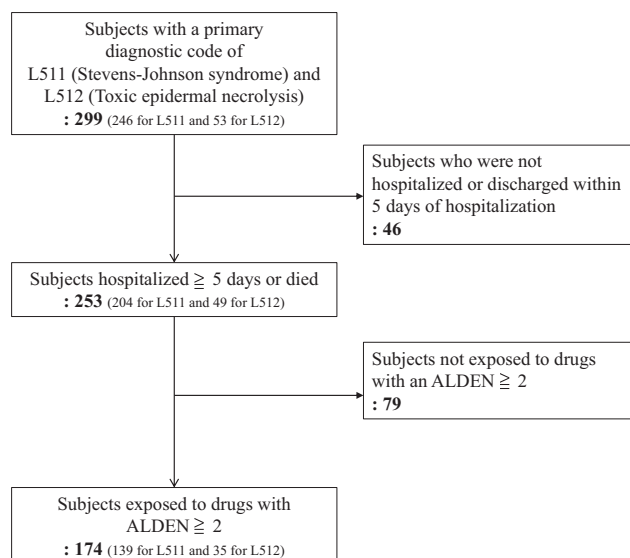


FIGURE 1. Flowchart for the subject selection process. *ALDEN*, Algorithm for assessment of drug causality for epidermal necrolysis.

the probable index day was when the first SJS or TEN symptoms occurred. The probable index day should be used when identifying culprit drugs. We considered the first day of diagnosis of SJS or TEN or the first occurrence of a diagnosis of suspected prodrome as the index day. The medication prescribed, whether it was oral, parenteral, or topical, was assumed to be used as prescribed until the admission and then discontinued after hospitalization. The *ALDEN* score was calculated for each drug prescribed within 6 months before the index day in each subject. The drug with the highest score was identified as a culprit drug. If there were several drugs with the same score, we identified all of them as culprit drugs. Corticosteroids and antihistamines were excluded because of the high risk of false causal inferences, as those drugs could be administered for therapeutic purposes for SJS/TEN.

Statistical analysis

Most of the data were descriptive, as we used the entire South Korean population as the denominator. The ratio of the notoriety scores of the drugs in each *ALDEN* score was tested by linear-by-linear χ^2 analysis. IBM SPSS V.20.0 software (IBM Corp., Armonk, NY) was used for the analysis, and a *P* value of $<.05$ was considered significant. This study was approved by the Institutional Review Board of Seoul National University Boramae Medical Center (IRB No. 07-2016-25).

RESULTS

There were 246 and 53 subjects with the primary diagnostic codes L511 and L512, respectively. Among them, 46 cases were excluded because they were not hospitalized or were discharged within 5 days after hospitalization. Sixty-six subjects were not exposed to drugs with an *ALDEN* score ≥ 2 . Finally, 174 subjects were included in the analysis for culprit drugs (Figure 1). Among them, 160 subjects had 1, 12 had 2, 1 had 3, and 1 had 4 culprit drugs identified by the *ALDEN* score. The 4 culprit drugs for the last subject were bismuth subsalicylate, levosulpiride,

phloroglucinol, and sucralfate. The *ALDEN* score for those 4 drugs was 3.

Thirty-three drugs were very probable, 101 were probable, and 57 were possible culprit drugs for SJS and TEN. As expected, the *ALDEN* score increased as the notoriety of the drug increased ($P < .001$, Figure 2). Among 33 very probable drugs, carbamazepine was the most frequent (11 of 33) cause of SJS and TEN followed by allopurinol (9 of 33), lamotrigine (5 of 33), phenobarbital (2 of 33), sulfasalazine (2 of 33), meloxicam (1 of 33), piroxicam (1 of 33), sulfamethoxazole (1 of 33), and tramadol (1 of 33). No SJS or TEN cases were associated with the administration of nevirapine, sulfadiazine, sulfadoxine, sulfafurazole, or tenoxicam, which were included in the “strongly associated drugs” group from a previous case-control study.²

During the study period, 71 drugs were suspected to be culprit drugs for SJS and TEN in Korea (Table 1). Among them, allopurinol was the most frequent cause of SJS and TEN (19 cases), followed by carbamazepine (17 cases) and lamotrigine (13 cases). There were also ophthalmic drops, such as dorzolamide (9 cases), brinzolamide (3 cases), levofloxacin (2 cases), ofloxacin (3 cases), and pilocarpine (1 case). Sorting by the ATC code, S01EC (carbonic anhydrase inhibitors [CAIs]) was the most frequent cause of SJS and TEN, followed by M04AA (preparations inhibiting uric acid production), N03AF (carboxamide derivatives), and N03AX (other antiepileptics) (Table E1, available in this article’s Online Repository at www.jaci-inpractice.org). The time latency for the top 6 drugs from our cohort was visualized using a histogram (Figure 3). More than half of the cases associated with the administration of amoxicillin and acetaminophen occurred within 8 days of drug initiation. Most cases (78.8%, 52 of 66) associated with the use of allopurinol, carbamazepine, lamotrigine, dorzolamide, brinzolamide, and methazolamide occurred between 13 and 44 days after initiating the drug. The distribution of the age of onset for individual drugs was also examined (Figure E1, available in this article’s Online Repository at www.jaci-inpractice.org). SJS and TEN caused by allopurinol, carbamazepine, and CAIs occurred mainly in older people, whereas those caused by lamotrigine, amoxicillin, and acetaminophen occurred in subjects of any age.

DISCUSSION

In this study, we analyzed potential culprit drugs for SJS and TEN in Korea using a new methodology of applying the *ALDEN* score to the claims database. Through this approach, we present a list of drugs that might be the cause of SJS and TEN in Korea on a nationwide level.

Studying adverse drug reactions using a claims database has weak and strong points. The major weakness is that the diagnosis could be incorrect because researchers cannot directly review the medical records of the subjects.¹⁰ We excluded cases where the diagnosis of SJS and TEN was unlikely to reduce the risk of misdiagnosis. First, we excluded the cases in which the diagnosis changed during or after hospitalization because the diagnosis could be confused initially with a bullous skin disease, such as erythema multiforme, generalized bullous fixed drug eruption, or pemphigus.¹¹ Second, 46 cases who were not hospitalized or discharged within 5 days of hospitalization were excluded because the initial diagnosis was incorrect. Third, we limited our analysis only to cases that had suspicious culprit drugs identified through the *ALDEN* score. Among 253 possible SJS and TEN

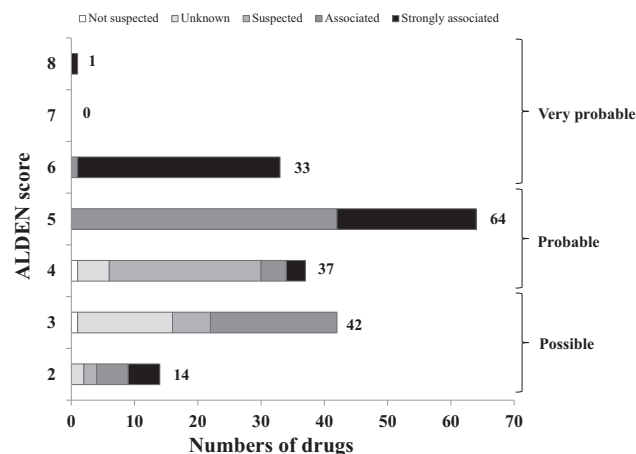


FIGURE 2. The distribution of ALDEN scores for the suspected culprit drugs with their notoriety for Stevens-Johnson syndrome and toxic epidermal necrolysis. ALDEN, Algorithm for assessment of drug causality for epidermal necrolysis.

cases, 79 (31.2%) cases were designated to be non-drug-related SJS and TEN. This was in line with the results of other studies reporting that 17% to 25% of SJS and TEN are non-drug-related SJS and TEN.^{9,12} On the other hand, the major advantage of using a claims database to study adverse drug reactions is that researchers can gather a wide range of drug prescriptions from a specific subject. In this study, we collected drug prescription data from the start of 2009 to the end of 2013 as we reported previously.⁷ There were 33 very probable, 101 probable, and 57 possible culprit drugs. Considering that it is often difficult to identify culprit drugs in real practice, we thought that our results, used to determine culprit drugs, were effective.

Plotting the distribution of the time latency of each drug helps to assess the relevance of the drug as the cause of SJS and TEN, in addition to application of the ALDEN score, as shown previously.^{2,13} A previous case-control study showed that the time latency for highly suspected drugs was aggregated between 4 and 28 days. In this study, the shapes of the latency curves for carbamazepine and CAIs were most typical, most of the cases were aggregated between 4 and 28 days of exposure, and peak incidence occurred after approximately 16 days of exposure. The curves for allopurinol and lamotrigine showed a longer latency period (most cases within 21 and 44 days) and late peak incidence (around 32 days), as compared with the typical shape. By contrast, those for amoxicillin and acetaminophen had a very short latency time, so that almost all cases were aggregated within the first 12 days of exposure. As these drugs are frequently prescribed for flu-like symptoms, there was a possibility that these drugs had been prescribed to treat the prodromal symptoms of SJS and TEN and they were not actual culprit drugs.⁹ On the other hand, considering that these drugs are commonly used drugs in the community, there was also the possibility that many people had become sensitized to the drugs¹⁴ and SJS/TEN caused by acetaminophen may have a short latency as reported previously.¹⁵ Therefore, these drugs may need to be investigated in the future.

The results of the analysis on culprit drugs for SJS and TEN in Korea, using the claims database, confirmed known high-risk medications and identified new culprit drugs. The most common

TABLE I. List of suspected culprit drugs in this study

No. of cases	Name of drugs
19	Allopurinol
17	Carbamazepine
13	Lamotrigine
9	Amoxicillin, dorzolamide
8	Acetaminophen
7	Methazolamide
5	Phenytoin, levofloxacin
4	Aceclofenac, cefaclor, ceftriaxone, diclofenac
3	Ambroxol, brinzolamide, bromhexine, cefuroxime, ciprofloxacin, ofloxacin (ophthalmic), tramadol
2	Acetylcysteine, cefpodoxime, itopride, lansoprazole, levofloxacin (ophthalmic), meloxicam, nizatidine, ofloxacin, piroxicam, sulfamethoxazole, sulfasalazine
1	Sucralfate, bismuth subsalicylate, cefcapene, cefixime, celecoxib, cephalixin, cefazidone, cimetidine, clarithromycin, clopidogrel, ethambutol, fluconazole, gabapentin, gemifloxacin, indobufen, isoniazid, levosulpiride, meropenem, montelukast, moxifloxacin, neomycin, omeprazole, pantoprazole, phenobarbital, phloroglucinol, pilocarpine ophthalmic, piperacillin, rabeprazole, rebamipide, rifaximin, roxatidine, roxithromycin, terazosin, terbinafine, tinidazole, tizanidine, vancomycin, verapamil, warfarin, zonisamide

causes of SJS and TEN in Korea, estimated using the claims database, were taking allopurinol, carbamazepine, or lamotrigine.^{2,16} These 3 drugs explained 49 of 174 (28.2%) of all SJS/TEN cases. In addition to the 3 well-known causes of SJS and TEN, CAIs were the most commonly suspected culprit drugs for Koreans. CAIs are used as antiglaucoma agents, and 4 types of CAIs are on the market in Korea, including acetazolamide, methazolamide, dorzolamide (topical), and brinzolamide (topical). CAIs including topical agents are known causes of SJS and TEN in the Korean, Japanese, and Chinese populations, and a genetic risk factor for CAI-induced SJS and TEN in Korean had been suggested.¹⁷⁻²⁰ Although the CAIs are well-known culprit medications for SJS and TEN in Korea, they were not nominated as strongly as associated non-anti-infective sulfonamides in previous case-control studies because they were not risky medications for other ethnic groups. In comparison, only 2 cases were suspected of being caused by anti-infective sulfonamides, 1 by phenobarbital, and none by nevirapine. The reason for the low incidence of SJS and TEN cases related to these drugs might be their low usage rates due to differences in the prescription pattern. For example, although 179,580 defined daily doses (DDDs) of trimethoprim-sulfamethoxazole (TMP-SMX), the only anti-infective sulfonamide available in Korea, were sold in 2011, which was much lower than the sales of top-ranked causative drugs (Table E2, available in this article's Online Repository at www.jaci-inpractice.org),²¹ the incidence of SJS and TEN per million TMP-SMX DDDs was 11.12, which was higher than those for the other top-ranked drugs. These results imply that the prescription pattern influences the level of exposure to a specific drug in the general population and consequently affects the incidence of SJS and TEN caused by that drug. The relationship between the level of exposure and the incidence of SJS and TEN was also supported by the age distribution of the SJS and TEN cases according to the causative

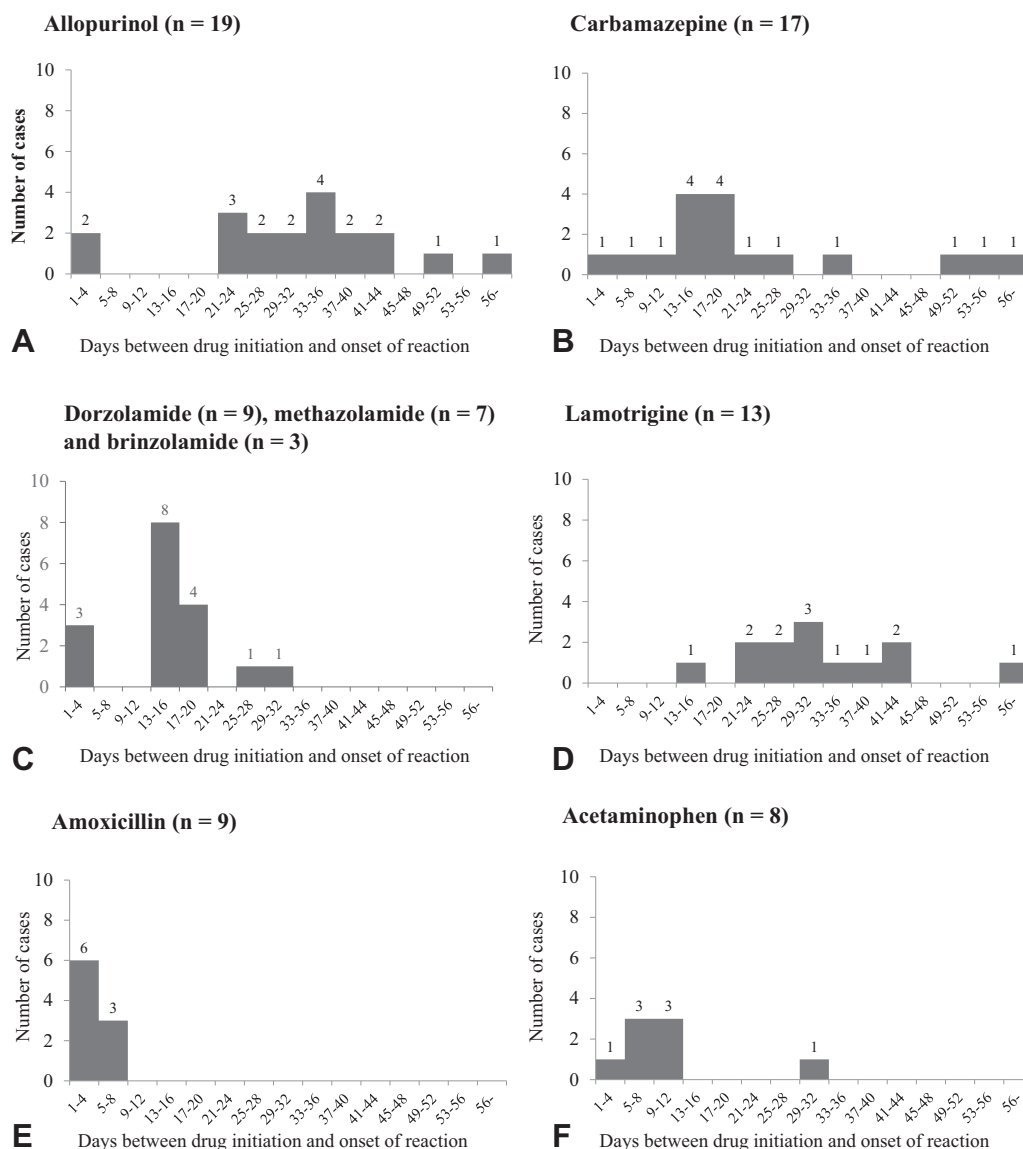


FIGURE 3. The time latency of top 6 suspected culprit drugs for Stevens-Johnson syndrome and toxic epidermal necrolysis. The latency of allopurinol (A) and lamotrigine (D) showed a longer latency period than carbamazepine (B) and carbonic anhydrase inhibitors (C). Amoxicillin (E) and acetaminophen (F) showed a very short latency period. (C) Two subjects used 2 different kinds of carbonic anhydrase inhibitors simultaneously.

drugs. SJS and TEN occurred more commonly in the age groups that might be likely to use the drugs more often than in other age groups (Figure E1, available in this article's Online Repository at www.jaci-inpractice.org). Therefore, the prescription pattern and ethnicity may need to be considered when applying the ALDEN score, and a case-control study of medication risk factors for SJS and TEN is needed for the population of interest.

Some limitations in the design of this study prevented us from confirming the diagnosis of the cases. We could not confirm subjects' diagnoses using photographs or pathology reports, as HIRA does not provide these materials because of the domestic information disclosure policy. Although we tried to reduce the risk of misdiagnosis, as discussed above, the selection of subjects based on diagnostic codes alone could result in many errors.^{1,22} Nevertheless, we believe that we had fewer miscoded cases than

in previous studies based on ICD-9 codes, as codes for SJS and TEN are distinct from those for other forms of erythema multiforme in the ICD-10 system.^{23,24} The diagnostic code L51.3 (SJS-TEN overlap syndrome) was not seen in any of the cases, as this code was only present in the ICD-10-CM (clinical modification) code and not in the original ICD-10 code. Because the ICD-10-CM code is used only in the United States and not in Korea, the L51.3 code was not applied in this study. We excluded patients who were hospitalized for fewer than 5 days. Thus, the possibility that mild cases of SJS were excluded could not be ruled out. However, we believe that the advantage of excluding misdiagnosed cases through the application of this criterion outweighs the drawback of excluding milder cases. We were also unable to collect information on over-the-counter drug use. In addition, we could not identify the level of exposure to a

specific drug in the entire population or by age group because we could not obtain data on the annual sales volumes of all drugs included in the analysis. Nevertheless, such an approach is valuable, particularly for national policymaking. As we showed in this study, some drugs causing SJS and TEN may be limited to certain ethnic groups. Although only a 1-year-period was investigated in this study, additional suspected culprit drugs for SJS and TEN could be identified by applying the same methodology over a longer time frame. This would eliminate a probable year-specific bias. Nevertheless, this analysis was limited to 1 year to reduce potential bias due to the differences between the pre-challenge and rechallenge periods among subjects. Considering the difficulties involved in conducting a large cohort study of SJS and TEN, our method may offer a good alternative approach for selecting and monitoring possible at-risk drugs.

In conclusion, we applied the ALDEN score to the claims database to select possible culprit drugs for SJS and TEN in Korea. This approach could shed light on research and policy-making for drug adverse reactions.

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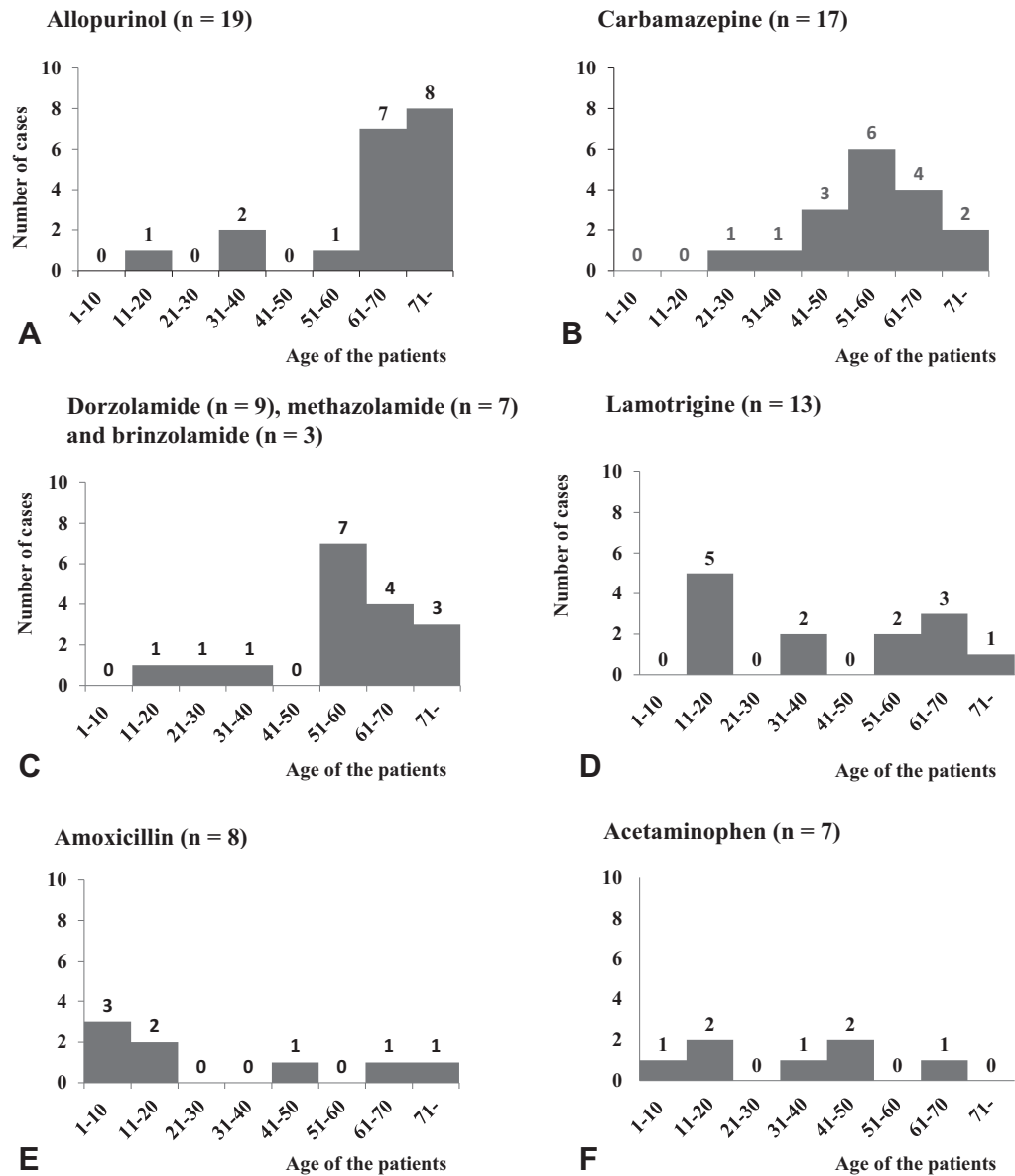


FIGURE E1. The age of patients of top 6 suspected culprit drugs for Stevens-Johnson syndrome and toxic epidermal necrolysis. Stevens-Johnson syndrome and toxic epidermal necrolysis caused by allopurinol (**A**), carbamazepine (**B**), and carbonic anhydrase inhibitors (**C**) occurred in older subjects than those by lamotrigine (**D**), amoxicillin (**E**), and acetaminophen (**F**).

TABLE E1. List of suspected culprit drugs in this study by the ATC classification system

No. of cases	ATC code
20	S01EC (carbonic anhydrase inhibitors)
19	M04AA (preparations inhibiting uric acid production)
17	N03AF (carboxamide derivatives)
15	N03AX (other antiepileptics)
12	J01MA (fluoroquinolones)
10	J01CA (penicillins with extended spectrum)
8	J01DD (third-generation cephalosporins), N02BE (anilides), R05CB (mucolytics), M01AB (acetic acid derivatives and related substances)
7	J01DC (second-generation cephalosporins)
6	S01AE (fluoroquinolones [ophthalmic])
5	A02BC (proton pump inhibitors), N03AB (hydantoin derivatives)
4	A02BA (H2-receptor antagonists), M01AC (oxicams)
3	A07AA (antibiotics), N02AX (other opioids)
2	A03FA (propulsives), A07EC (aminosalicylic acid and similar agents), B01AC (platelet aggregation inhibitors excl. heparin), J01DB (first-generation cephalosporins), J01EC (intermediate-acting sulfonamides), J01FA (macrolides)
1	A02B (drugs for peptic ulcer and gastro-oesophageal reflux disease [GORD]), A02BX (other drugs for peptic ulcer and GORD), A03AX (other drugs for functional gastrointestinal disorders), B01AA (vitamin K antagonists), C08DA (phenylalkylamine derivatives), D01AC (imidazole and triazole derivatives), D01AE (other antifungals for topical use), G03AC (progestogens), G04CA (alpha-adrenoreceptor antagonists), J01DH (carbapenems), J01XD (imidazole derivatives), J04AC (hydrazides), J04AK (other drugs for treatment of tuberculosis), M01AH (coxibs), M03BX (other centrally acting agents), N03AA (barbiturates and derivatives), R03DC (leukotriene receptor antagonists), S01EB (parasympathomimetics)

ATC, Anatomical Therapeutic Chemical.

TABLE E2. Incidence of SJS and TEN by top-ranked causative drugs by annual sales volume

	SJS and TEN (n)	Annual sales volume in 2011* (defined daily dose)	Incidence of SJS and TEN (per million doses)
Allopurinol	19	15,461,676	1.23
Carbamazepine	17	14,158,327	1.20
Lamotrigine	13	5,782,594	2.25
Amoxicillin	9	191,593,000	0.05
Dorzolamide	9	813,609	11.06
Acetaminophen	8	164,519,448	0.04
Methazolamide	6	250,322	23.97

SJS, Stevens-Johnson syndrome; TEN, toxic epidermal necrolysis.

*The data on the annual sales volume in 2011 of individual drugs were publicly accessible at the time of study.