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Original Article

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Phenotypes of Severe Cutaneous Adverse Reactions Caused by Nonsteroidal Anti-inflammatory Drugs

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ABSTRACT

Purpose: Nonsteroidal anti-inflammatory drugs (NSAIDs) are common cause of severe cutaneous adverse reactions (SCARs). The present study aimed to investigate the characteristics of SCARs induced by NSAIDs in the Korean SCAR registry.
Methods: A retrospective survey of NSAID-induced SCARs recorded between 2010 and 2015 at 27 university hospitals in Korea was conducted. Clinical phenotypes of SCARs were classified into Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), SJS-TEN overlap syndrome and drug reaction with eosinophilia and systemic symptoms (DRESS). Causative NSAIDs were classified into 7 groups according to their chemical properties: acetaminophen, and propionic, acetic, salicylic, fenamic and enolic acids.

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There are no financial or other issues that might lead to conflict of interest.

Results: A total of 170 SCARs, consisting of 85 SJS, 32 TEN, 17 SJS-TEN overlap syndrome and 36 DRESS reactions, were induced by NSAIDs: propionic acids (n=68), acetaminophen (n=38), acetic acids (n=23), salicylic acids (n=16), coxibs (n=8), fenamic acids (n=7), enolic acids (n=5) and unclassified (n=5). Acetic acids (22%) and coxibs (14%) accounted for higher portions of DRESS than other SCARs. The phenotypes of SCARs induced by both propionic and salicylic acids were similar (SJS, TEN and DRESS, in order). Acetaminophen was primarily associated with SJS (27%) and was less involved in TEN (10%). DRESS occurred more readily among subjects experiencing coxib-induced SCARs than other NSAID-induced SCARs (62.5% vs. 19.7%, $P = 0.013$). The mean time to symptom onset was longer in DRESS than in SJS or TEN (19.1 ± 4.1 vs. 6.8 ±1.5 vs. 12.1 ± 3.8 days). SCARs caused by propionic salicylic acids showed longer latency, whereas acetaminophen- and acetic acid-induced SCARs appeared within shorter intervals.
Conclusions: The present study indicates that the phenotypes of SCARs may differ according to the chemical classifications of NSAIDs. To establish the mechanisms and incidences of NSAID-induced SCARs, further prospective studies are needed.

Keywords: Anti-Inflammatory Agents, Non-Steroidal; Drug Hypersensitivity; Stevens-Johnson Syndrome

INTRODUCTION

The most common manifestation of adverse reactions to a drug is cutaneous presentation,[1] such as urticaria, angioedema, fixed drug eruption or maculopapular rash. Of these, 2% are severe, and a few even end in fatalities.[2] Severe cutaneous adverse reactions (SCARs) include Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), drug reaction with eosinophilia and systemic symptoms (DRESS) and acute generalized exanthematous pustulosis. SCARs can be life-threatening, with mortality rates ranging from 23% to 45% for patients with TEN and 10% for those with DRESS.[3,4]

Nonsteroidal anti-inflammatory drugs (NSAIDs) are among the most frequently used medications worldwide, and they are thought to be leading causative agents of drug adverse reactions.[5,6] Alteration in arachidonic acid metabolism by cyclooxygenase (COX) inhibition has been proposed as a major mechanism of NSAID-induced urticaria/angioedema or anaphylaxis.[7,8] NSAIDs can also induce selective immediate reactions mediated by IgE,[9] such as SCARs which arise after T-cell responses.[10,11] In cases of NSAID-induced immediate hypersensitivity, such as asthma, urticaria, angioedema and anaphylaxis, a wide spectrum of cross-reactions among NSAIDs is well known. However, there is a lack of evidence concerning the cross-reactivity of different NSAIDs in cases of delayed hypersensitivity to NSAIDs, such as SCARs. The characteristics of SCARs induced by individual classes of NSAIDs have only been studied in a small series or individual case reports, although the majority of NSAID-induced delayed hypersensitivity reactions are not mediated by a common pharmacodynamics profile shared by NSAIDs. This study was designed to obtain information on clinical differences in the characteristics of SCARs according to the classes of culprit NSAIDS.

MATERIALS AND METHODS

Subject selection

A total of 745 SCAR cases were selected from 34 hospitals through a retrospective review of medical records spanning 6 years; among them, 170 were SCARs induced by NSAIDs. In

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order to find suspicious cases, a database of adverse drug reactions, medical record diagnosis and related referral records were all investigated with reference to inclusion criteria of the registry of severe cutaneous adverse reaction group.[12,13] Selected cases were registered if 2 doctors, including 1 who was an allergy specialist, concurred with the SCAR diagnosis. To register each case, all medical records were reviewed, and data on demographics, hospitalization, vital signs, laboratory results, clinical courses, and disease and medication histories were entered (**Supplementary Fig. S1**). According to their clinical manifestations, patients were classified into 4 disease categories: SJS, SJS-TEN overlap syndrome, TEN or DRESS. Patients diagnosed with one of the following were excluded: pemphigus, erythema multiforme, bullous pemphigoid, staphylococcal scalded skin syndrome, mechanobullous eruption (heat, cold, friction, pressure), acute pustular psoriasis, Kawasaki's disease, toxic shock syndrome, graft-versus-host disease, vasculitis and epidermolysis bullosa. This study was approved by the Institutional Review Board of the Seoul National University Hospital (IRB No. H-1408-021-601).

Causality assessment

Drug exposure was calculated based on prescription data in defined daily doses. The causalities of suspected drugs and SCAR were assessed by the World Health Organization-Uppsala Monitoring Centre causality categories.[14] The analysis included "certain" and "probable" cases of SCARs due to NSAIDs. All medical records were thoroughly reviewed, and data such as demographics, hospitalization, vital signs, laboratory results, clinical course, disease history and medication history were entered into a standardized clinical record form. The validity of the input data was confirmed after discussion with the Korea Institute of Drug Safety & Risk Management and SCAR Special Interest Group.

Classification of culprit NSAIDs

Among 170 cases judged as SCARs induced by NSAIDs, causative NSAIDs were classified into 7 groups according to their chemical properties: propionic acids (dexibuprofen, ibuprofen, loxoprofen, naproxen, zaltoprofen), acetaminophen, acetic acids (aceclofenac, diclofenac, etodolac, ketorolac, sulindac), salicylic acids (aspirin, morniflumate, talniflumate), coxibs (celecoxib), fenamic acids (mefenamic acid) and enolic acids (meloxicam, piroxicam). They were categorized as "unclassified" if the reactions were obviously due to NSAIDs but there was no information on the specific name of NSAID.

Statistical analysis

The demographic data are presented as means ± standard deviation if normally distributed. Categorical variables are presented as frequencies with percentages. Continuous variables were analyzed using a *t* test or Mann-Whitney *U* test based on normality, and categorical data were compared using Pearson's χ^2 test or Fisher's exact test. A 2-sided *P* value <0.05 was considered significant. All statistical tests were performed using IBM SPSS Statistics, version 24.0 (SPSS Inc., Chicago, IL, USA).

RESULTS

Culprit NSAIDs among the study subjects

Among the 170 cases of SCAR, common culprit NSAIDs included propionic acids (68 cases), acetaminophen (38 cases), acetic acids (23 cases), and salicylic acids (16 cases). Fewer than 10 cases each were induced by coxibs (8 cases), fenamic acids (7 cases), and enolic acids (5 cases)

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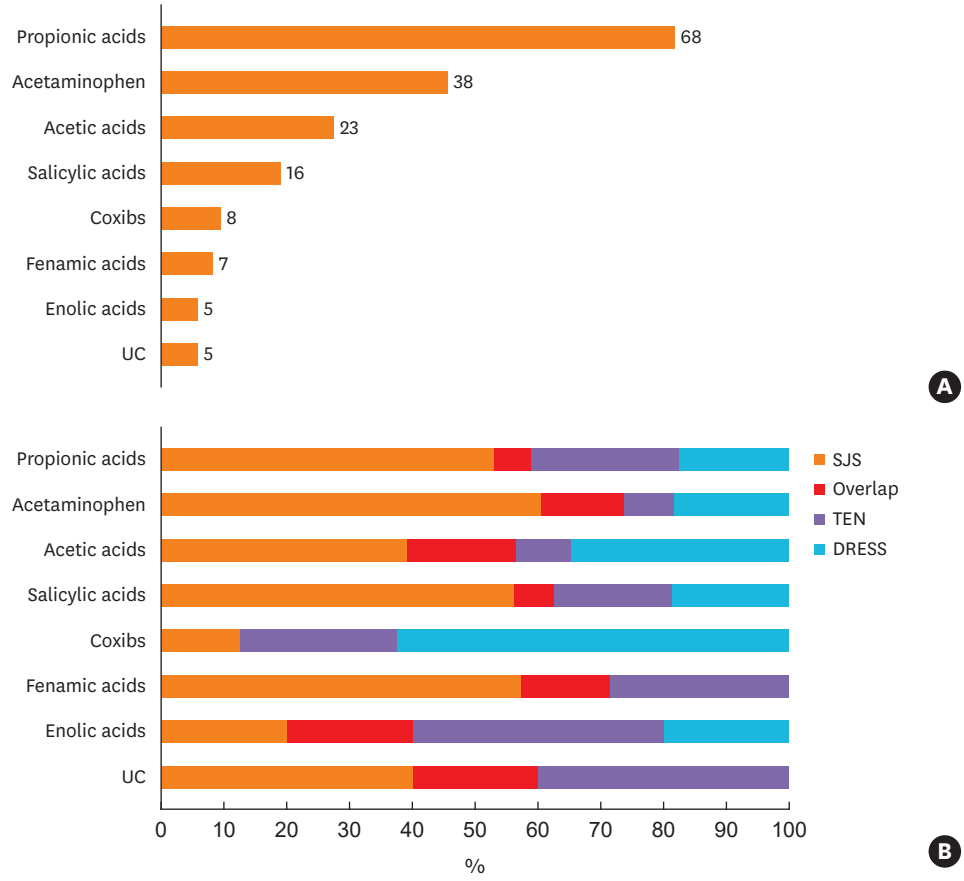

Fig. 1. Distribution of subjects according to culprit NSAID class (A) and the proportions of SCAR phenotypes according to NSAID class (B).
NSAID, nonsteroidal anti-inflammatory drug; SCAR, severe cutaneous adverse reaction; UC, unclassified.

(**Fig. 1A**). DRESSs were significantly more frequent in subjects experiencing coxib-induced SCARs than in those with SCARs induced by other NSAIDs (62.5% vs. 19.7%, $P = 0.013$; **Fig. 1B**). No DRESS was recorded in subjects with SCARs caused by fenamic acids. TEN occurred less frequently with acetaminophen (7.9% vs. 21.3%, $P = 0.045$; **Fig. 1B**) than with other drug classes. TEN cases were most common in individuals treated with enolic acids (40.0%).

Distribution of culprit NSAIDs and clinical characteristics according to SCAR phenotype

Among the 170 subjects with NSAIDs-induced SCARs, 134 (78.8%) presented with SJS (85 subjects), SJS-TEN overlap (32 subjects) or TEN (17 subjects); the remaining 36 (21.2%) were diagnosed with DRESS (**Fig. 2**). Propionic acid was the predominant NSAID class in SJS, SJS-TEN overlap and TEN. Acetaminophen (27%) was a common culprit drug in SJS, but less so in TEN (10%). Among patients experiencing DRESS, acetic acids (22%) and coxibs (14%) accounted for higher proportions of adverse reactions relative to other SCAR types.

In terms of clinical characteristics according to SCAR phenotype, mean age was higher in the TEN group than in the SJS group (57.7 ± 3.6 vs. 41.8 ± 2.6 years, $P = 0.001$; **Table 1**). Mean Body mass index (BMI) was highest in the DRESS group, compared with the other SCAR groups combined (24.0 ± 0.7 kg/m^2 vs. 21.9 ± 3.8 kg/m^2, $P = 0.011$). Accompanying mucosal involvement did not differ between SJS and TEN (88.9% vs. 80.8%, $P = 0.226$). Body

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Fig. 2. Proportions of culprit NSAIDs according to SCAR phenotype.
NSAID, nonsteroidal anti-inflammatory drug; SCAR, severe cutaneous adverse reaction; UC, unclassified; DRESS, drug reaction with eosinophilia and systemic symptoms; SJS, Stevens-Johnson syndrome; TEN, toxic epidermal necrolysis.

surface areas of involved skin, serum creatinine levels and serum alanine aminotransferase levels were higher in the TEN and DRESS groups than in the other SCAR groups. The duration of hospital stay (34.3 ± 4.8 vs. 14.6 ± 0.9 days, $P = 0.001$) and the use of intravenous

Table 1. Demographics and clinical presentations of SCARs according to phenotype

	SJS (n=85)	Overlap (n=32)	TEN (n=17)	DRESS (n=36)	*P* value
Age	41.8 ± 2.6	49.4 ± 4.4	57.7 ± 3.6	54.3 ± 3.0	0.002
Sex (% of males)	38.8	52.8	50	33.3	0.375
BMI (kg/m^2)	21.8 ± 0.5	22.9 ± 0.9	21.7 ± 0.6	24.0 ± 0.7	0.042
Presenting symptoms					
Mucosal involvement (%)	88.9	78.6	80.8	35.7	0.001
Involved BSA (%)	64.9 ± 3.8	55.4 ± 8.5	73.7 ± 5.1	86.6 ± 4.0	0.015
Fever (%)	46.3	53.3	56.7	61.8	0.454
Increased creatinine (%)	4.7	11.8	25	25	0.004
Increased ALT (%)	48.2	58.8	71.9	77.8	0.009
Duration of steroid use (day)	14.6 ± 1.9	14.6 ± 2.8	21.3 ± 4.7	12.2 ± 2.1	0.650
Total dose of methyl-prednisolone (mg)	1,184.8 ± 272.3	1,582.8 ± 689.8	1,859.4 ± 589.5	857.7 ± 177.3	0.640
Duration of hospitalization	12.9 ± 1.0	21.7 ± 2.5	34.3 ± 4.8	15.3 ± 2.4	0.001
Use of IVIG (%)	9.4	11.8	59.7	5.6	0.001
Prognosis					0.001
Improved	84.3	75	53.1	97.1	
With sequelae	15.7	6.3	34.4	2.9	
Death	0	18.8	12.5	0	

SCAR, severe cutaneous adverse reaction; SJS, Stevens-Johnson syndrome; overlap, combined Stevens-Johnson syndrome and toxic epidermal necrolysis; TEN, toxic epidermal necrolysis; DRESS, drug reaction with eosinophilia and systemic symptoms; BMI, body mass index; BSA, body surface area; ALT, alkalne phosphatase; IVIG, intravenous immunoglobulin.

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immunoglobulin (57.9% vs. 8.7%, $P = 0.001$) was higher in the TEN group than in the other SCAR groups. Although SCAR-related mortality rate was difficult to analyze accurately due to the small number of mortality cases, the portion of cases that recovered without any sequelae was highest in the DRESS group.

Demographics and clinical presentations of SCARs according to NSAID classification

Subject age, sex or BMI showed no statistically significant differences according to NSAID classification (**Table 2**). Mucosal involvement was recorded in all subjects presenting with enolic acids-induced SCARs. However, the mean extent of skin involvement was smallest for enolic acid-induced SCARs, compared to SCARs induced by other drugs (31.3% ± 9.3%, vs. 70.9% ± 2.6%, $P = 0.015$). The proportion of subjects presenting with fever, increased creatinine levels and increased alkaline transferase levels was highest in the coxib group, compared to the other NSAID groups. Both the mean duration and total dose of steroid use were lowest in the enolic acid group, although statistical significance was lacking. Intravenous immunoglobulin use was also most frequently recorded in the coxib group.

Time interval between initiation of drug and onset of symptoms

Time to symptom onset differed among the SCAR phenotypes. In the DRESS group, the mean time to symptom onset was longer than those for SJS and TEN (19.1 ± 4.1 vs. 6.8 ±1.5 days for SJS, 12.1 ± 3.8 days for TEN). However, even within the same phenotype of SCARs, there were also differences in time between drug exposure and symptom onset according to the classification of NSAIDs (**Fig. 3**).

Table 2. Demographics and clinical presentations of SCARs according to NSAID class

	Propionic Acids (n=68)	Acetaminophen (n=38)	Acetic Acids (n=23)	Salicylic Acids (n=16)	Coxibs (n=8)	Fenamic Acids (n=7)	Enolic Acids (n=5)
Age	22.4 ± 0.4	21.4 ± 0.8	24.4 ± 1.1	21.2 ± 1.0	22.0 ± 1.2	24.0 ± 0.8	23.0 ± 3.5
Sex (% of males)	44.1	36.5	21.7	56.3	37.5	57.1	
BMI (kg/m^2)	22.4 ± 0.4	21.4 ± 0.8	24.4 ± 1.1	21.2 ± 1.0	22.0 ± 1.2	24.0 ± 0.8	23.0 ± 3.5
Causality assessment (% of probable, or certain)	63.2	60.5	87	62.5	50	28.6	60
Presenting symptoms							
Mucosal involvement (%)	81.5	75.0	76.5	75.0	50.0	57.1	100.0
Involved BSA (%)	74.8 ± 3.5	72.2 ± 5.4	63.5 ± 8.2	50.2 ± 10.7	77.1 ± 8.2	83.7 ± 6.5	31.3 ± 9.3
Fever (%)	56.7	47.4	52.2	33.3	75.0	42.9	33.3
Increased creatinine (%)	13.2	5.3	26.1	18.8	25.0	0.0	20.0
Increased ALT (%)	63.2	57.9	56.5	50.0	75.0	57.1	60.0
Days of steroid use	19.1 ± 2.7	11.4 ± 2.0	11.2 ± 2.0	14.4 ± 5.4	15.9 ± 5.1	14.3 ± 2.8	9.2 ± 3.0
Total dose of methyl-prednisolone (mg)	1,613.5 ± 331.0	841.0 ± 206.3	524.5 ± 277.2	1,196.7 ± 707.8	1,004.3 ± 406.3	1,268.3 ± 680.1	405.2 ± 163.4
Duration of steroid use/hospital day	1.02	0.65	0.60	1.01	0.54	0.96	0.74
Duration of steroid use/hospital day × 100	102.2	64.6	60.1	100.8	53.6	95.6	74.2
Use of IVIG (%)	17.6	18.4	13.0	12.5	50.0	28.6	20.0
Duration of disease (day)	24.5 ± 2.3	21.5 ± 2.9	23.0 ± 2.8	25.6 ± 1.4	28.1 ± 8.6	17.4 ± 3.3	24.0 ± 4.4
SJS-TEN/DRESS	25.3/20.8	22.4/17.6	22.7/23.7	23.6/33.0	31.3/26.2	17.4/-	24.0/NA
Duration of hospitalization (day)	18.7 ± 2.4	17.6 ± 2.5	18.7 ± 2.9	14.3 ± 2.6	29.6 ± 9.1	15.0 ± 3.5	12.4 ± 5.7
SJS-TEN/DRESS	20.1/12.1	18.6/13.1	20.4/15.4	15.0/11.3	26.3/31.6	15.0/-	12.4/NA
Rate of ICU admission (%)	10.9	8.1	8.7	0.0	0.0	0.0	0.0
SJS-TEN/DRESS	13.0/0.0	10.0/0.0	13.3/0.0	0.0/0.0	0.0/0.0	0.0/-	0.0/0.0
Mortality rate (%)	4.5	0.0	8.7	6.3	0.0	0.0	20.0
SJS-TEN/DRESS	4.5/0.0	0.0/0.0	13.3/0.0	7.7/0.0	0.0/0.0	0.0/-	25.0/0.0

SCAR, severe cutaneous adverse reaction; NSAID, nonsteroidal anti-inflammatory drug; BMI, body mass index; BSA, body surface area; ALT, alkaline transferase; IVIG, intravenous immunoglobulin; SJS, Stevens-Johnson syndrome; TEN, toxic epidermal necrolysis; DRESS, drug reaction with eosinophilia and systemic symptoms; ICU, intensive care unit; NA, not available.

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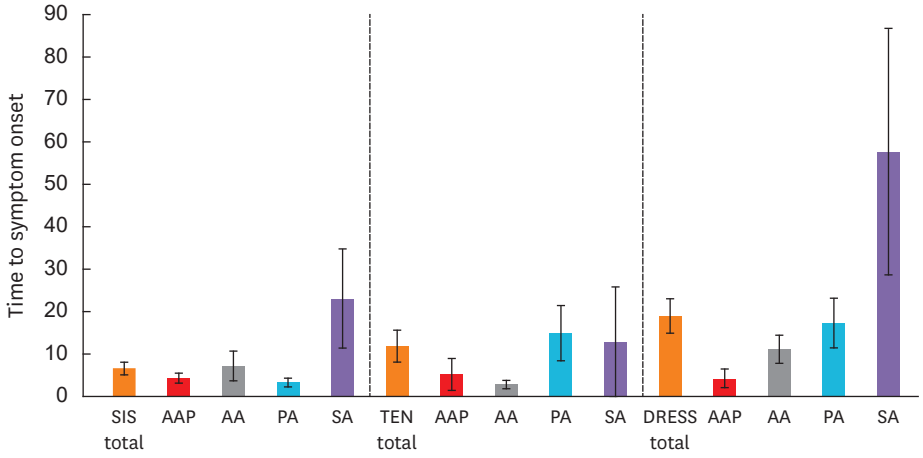

Fig. 3. Time interval between initiation of drug and onset of symptoms according to culprit NSAID.
NSAID, nonsteroidal anti-inflammatory drug; UC, unclassified; SJS, Stevens-Johnson syndrome; TEN, toxic epidermal necrolysis; DRESS, drug reaction with eosinophilia and systemic symptoms; AAP, acetaminophen; AA, acetic acid; PA, propionic acid; SA, salicylic acid.

We also noted a slight difference in latency among the causative agents of the same clinical symptoms. Subjects with SCARs induced by propionic acids and salicylic acids showed longer times to symptom onset, whereas SCARs stemming from acetaminophen and acetic acids use appeared within shorter times. The statistical significance in these differences among the drug classes for each SCAR phenotype was not considered due to the small numbers in each category.

Prognosis of SCARs according to NSAID classification

The durations of SCARs and hospitalization did not differ among the NSAID classes (**Table 2**). Among 170 subjects, 12 were treated in an intensive care unit (ICU). The mean duration of ICU hospitalization was 18 days. Six of these 12 subjects experienced TEN; the rest presented with SJS (5 cases) and SJS-TEN overlap (1 case). The most common culprit NSAIDs leading to serious SCARs that necessitated treatment in an ICU were propionic acids (7/12), followed by acetaminophen (3/12) and acetic acids (2/12). Three subjects (2 with TEN and 1 with SJS-TEN overlap) died during ICU admission. Among all 170 cases, 7 involved mortality, including 4 with TEN and 3 with SJS-TEN overlap. Of these 7, 3 were associated with propionic acid, and 2 were affected by acetic acids.

DISCUSSION

In the present study, although propionic acids were the most commonly used NSAIDs, the proportions of TEN and DRESS were relatively smaller for propionic acids than for other NSAIDs. Interestingly, despite being recognized as commonly inducing SJS/TEN, enolic acids were the least frequent causative agents of SCARs in the present study: Oxicam, an enolic acid in our classification, was found to be as the most common NSAID inducing SJS/TEN in European studies,[15,16] and another article indicated that enolic acids pose higher risks of SJS and TEN than other NSAIDs.[17] Notwithstanding, the time interval between exposure to the culprit drug and symptom onset was longest for SCARs induced by enolic acids than for other NSAID-induced SCARs. Moreover, enolic acid-induced SCARs were frequently accompanied by mucosal involvement. Coxib-induced SCARs were predominantly manifested as DRESS

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and showed longer days of hospitalization. SCARs induced by acetaminophen were mostly mild SJS characterized by a relatively short latency period until symptom onset.

Only a few studies have described the characteristics of hypersensitivity reactions according to specific classifications of NSAIDs. IgE-mediated selective reactions are known to be more common for pyrazolones and ibuprofen,[18,19] and delayed reactions are considered common with pyrazolones, propionic acids and acetic acids.[20] There are fewer studies on SCARs induced by NSAIDs. To our knowledge, the present study is the first to provide information on SCAR phenotypes according to individual classes of NSAIDs.

The mechanism by which SCARs are induced by NSAIDs is not completely understood yet. In general, the major type of hypersensitivity reactions to NSAIDs is cross-intolerant, which is related to an imbalance in the arachidonic acid pathway that leads to COX-1 inhibition. Most cross-intolerance reactions are immediate ones such as acute urticaria, angioedema and anaphylaxis. In delayed-type hypersensitivity reactions, T lymphocytes are known to play a key role in the pathogenesis thereof,[21] and selective reactions to NSAIDs are thought to be due to immunological mechanisms.[9,18,21] SCARs elicited by NSAIDs are generally likely to be selective reactions. To distinguish between cross intolerance and selective reactions, tolerability to aspirin should be demonstrated, and if a patient tolerates aspirin, a reaction can be deemed selective, even if it occurs in response to several NSAIDs.[22,23] However, even in selective responses, there can be cross reactivity between NSAIDs due to similarities in their chemical properties, as seen in adverse reactions induced by ß-lactams, which share a common ring and show cross reactivity between drugs. The results of the current study on the phenotypes of SCARs according to the chemical classes of NSAIDs are meaningful in that NSAIDs can also be classified into drug families with similar chemical structures.[9,21]

Coxibs, selective COX-2 inhibitors, were developed with the belief that they would be safer than other NSAIDs eliciting weak COX-1 inhibition. However, they have not been found to be free of safety concerns in regards to severe cutaneous reactions including DRESS and SJS, and some drugs have been voluntarily withdrawn from the market. Although coxibs exhibit a protective effect against cross intolerance by COX-1 inhibition, its safety does not apply to T-cell-specific responses. In a previous study, a strong association was noted between SJS/TEN and the use of the sulfonamide COX-2 inhibitors, particularly valdecoxib.[24] In the present study, DRESS was more common among coxib-induced SCARs. In these patients, increased serum creatinine levels and abnormal liver function were more common, and hospital stays were longer, compared to those in patients with other NSAID-induced SCARs. Differences in the mechanism of SCAR induced by coxibs and NSAIDs may be considered as a basis for COX-2 expression on T cells and upregulation by T-cell activation, unlike COX-1.[25] For comparison, acetaminophen appeared to be relatively safe in our study, and SCARs induced by acetaminophen exhibited relatively mild symptoms. These manifestations of acetaminophen-induced SCARs were likely affected by a short incubation period and short exposure time thereto.

Our investigation has some limitations. First, this study only included cases with adverse reactions, and incidence could not be calculated because there was no information on total numbers of cases in which a specific drug was used. This made it difficult to accurately assess risk. Secondly, because the reactions studied in this study were severe and life-threatening, re-administration or provocation test was not ethically viable. Therefore, oral provocation to confirm causality was not performed in most of the cases studied. Thirdly, the number of

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patients in some drug classification groups was too small to draw statistical significance. In particular, it was difficult to analyze the prognosis of rare events such as death or ICU admission. Finally, the exact mechanism for the appearance of SCARs induced by NSAIDs could not be elucidated through the present study.

In conclusion, the present study demonstrated that the clinical phenotypes of NSAID-induced SCARs many among the pharmaceutical classifications of NSAIDs. Collecting information on the accurate history of NSAID exposure is important for establishing causality of a culprit drug, as well as for determining safe alternatives for individuals who have experienced NSAIDs-induced SCARs. Further investigations of related mechanisms and incidence are warranted.

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SUPPLEMENTARY MATERIAL

Supplementary Fig. S1
Basic epidemiology of SCAR patients in Korea.

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