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Original Article

Severe Cutaneous Adverse Reactions to Anti-tuberculosis Drugs in Korean Patients

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ABSTRACT

Purpose: Anti-tuberculosis drugs (ATDs) can cause severe cutaneous adverse reactions (SCARs) such as Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), and drug reaction with eosinophilia and systemic symptoms (DRESS). Underlying tuberculous infection and co-administration of multiple drugs may contribute to the complexity of ATD-related SCARs. This study aimed to investigate the clinical characteristics and outcomes of ATD-related SCARs.
Methods: We analyzed ATD-related SCAR cases in 2010-2015, selected from a web-based Database of the Korean Registry of SCAR.
Results: Among 783, 53 patients with ATD-induced SCARs were enrolled, including 12 with SJS/TEN (22.6%) and 41 with DRESS (77.4%). When comparing the ATD and non-ATD groups, the prevalence of DRESS patients was higher in the ATD group than in the non-ATD group (77.4% vs. 45.8%, $P < 0.001$). Among patients with ATD-related SCARs, those with SJS/TEN were significantly older, had higher intensive care unit admissions, and had higher mortality than those with DRESS (70.5 vs. 50.0 years, $P < 0.001$; 41.7% vs. 6.1%, $P = 0.010$; and 33.3% vs. 2.5%, $P = 0.003$, respectively). ATDs were challenged in 14 cases. The ATD associated most often with SCAR cases was rifampin (81.8%), followed by isoniazid (66.7%), ethambutol (50.0%), pyrazinamide (33.3%). Six patients (42.9%) had hypersensitivity reactions to 2 or more drugs.

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

Conclusions: DRESS was more common among the ATD-related SCAR cases. Although treatment with most ATDs carries the risk of SCAR development, the use of rifampin was most frequently involved in the occurrence of SCARs. Multiple hypersensitivity was frequently observed in ATD-related SCARs.

Keywords: Antitubercular agents; severe cutaneous adverse reactions; Stevens-Johnson syndrome; toxic epidermal necrolysis; drug reaction with eosinophilia and systemic symptoms; drug hypersensitivity syndrome; skin; isoniazid; rifampin

INTRODUCTION

Tuberculosis is an infectious disease caused by *Mycobacterium tuberculosis.* According to a 2015 World Health Organization (WHO) report, the global prevalence of tuberculosis was 142 per 100,000 people.[1] Tuberculosis chemotherapy is complicated by the need for long-term multidrug regimens which are related to diverse adverse drug reactions (ADRs).[2] In addition, ADRs are one of the most common causes of treatment failure.

Common ADRs associated with anti-tuberculosis drugs (ATDs) include hepatitis, influenza-like illness, arthralgia, and cutaneous reactions.[3] Among various ATD-related ADRs, immunologically mediated severe forms, such as Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), and drug reactions with eosinophilia and systemic symptoms (DRESS), are designated as severe cutaneous adverse reactions (SCARs).[4] Although ATD-related SCARs are rare, affected cases have steadily been reported in the literature[5-8] and an increase in the reported number of ATD-associated DRESS cases has been observed over the past few years.[5] However, the clinical features and outcomes of SCARs related with ATDs have not yet been completely assessed.

Therefore, the aim of the present study was to investigate the characteristics and outcomes of ATD-associated SCARs and to evaluate clinical differences between patients with ATD-associated DRESS and SJS/TEN.

MATERIALS AND METHODS

Data collection and study subjects

Established in 2014, the Korean registry of SCARs includes 36 referral hospitals and enrolled SCAR cases (indicated by allergy specialists) occurring between 2010 and 2015.[9] Clinical information, causative drugs, and the causal relationship between offending drug and the reactions were assessed by allergy specialists at each hospital, and pharmacovigilant nurses reported information on affected patients to the online registry.[10] A diagnosis of SJS and TEN was based on the diagnostic criteria proposed by the RegiSCAR study group.[11] SJS/TEN cases were characterized by widespread exanthema or blisters with skin detachment. Inclusion criteria for DRESS cases were a suspected drug reaction with an acute skin rash, involvement of at least 1 internal organ, 1 blood abnormality, and fever > 38°C. Cases which met 3 or more of these criteria were considered DRESS.[12,13]

Data were obtained from patients who had SCARs related to ATDs including rifampin, isoniazid, ethambutol, pyrazinamide, cycloserine, prothionamide, and quinolones

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(levofloxacin and moxifloxacin). Causality was evaluated using the WHO-Uppsala Monitoring Centre causality assessment system, and cases were included if their causality was assessed as "certain," "probable," or "possible."[14,15] An algorithm for assessing drug causality (ALDEN) was applied to SJS/TEN.[16] For ATD-induced SJS/TEN and DRESS cases, we extracted and analyzed data on clinical manifestations, hospital course, causative ATD, time interval from the onset of symptoms to the day of diagnosis (disease period), time interval from drug exposure to the onset of symptoms (latent period), organ involvement, laboratory results, complications, and outcomes from the web registry. This study was approved by the Institutional Review Board of each institute (Pusan National University Hospital, E-2014125, etc.).

Statistical analysis

Data are presented as number (%) or median with range. Differences in study participants' characteristics were compared across subgroups using the χ^2 test or Fisher's exact test for categorical variables and the independent *t* test or the Mann-Whitney *U* test for continuous variables. To check if the data distribution was normal, we used the Shapiro-Wilk test. All statistical analyses were performed using SPSS 24.0 (SPSS, Chicago, IL, USA), and *P* values less than 0.05 were considered statistically significant.

RESULTS

Comparison of clinical characteristics between the ATD and non-ATD groups

Among 783 patients included in the registry, the study enrolled 53 (25 men, 28 women) with ATD-induced SCARs (**Table 1**). The prevalence of DRESS was higher in the ATD group than in the non-ATD group (77.4% vs. 45.8%, $P < 0.001$). Patients with SJS/TEN were significantly older in the ATD group than in the non-ATD group (70.5 vs. 54.0 years, $P < 0.001$). The latent period and disease duration of SCAR were significantly longer in the ATD group than in the non-ATD group. (27.0 vs. 14.0 days, $P = 0.002$, 29.0 vs. 20.0 days, $P = 0.003$, respectively).

The systemic corticosteroid administration rate was significantly lower in ATD patients than in non-ATD patients (66.0% vs. 85.1%, $P < 0.001$). Intensive care unit (ICU) hospitalization and mortality rates were significantly higher in the ATD group than in the non-ATD group (41.7% vs. 8.8%, $P = 0.001$ and 33.3% vs. 8.2%, $P = 0.011$, respectively).

Clinical characteristics according to the SCAR type in the ATD group

The study enrolled a total of 53 patients with ATD-induced SCARs, including 12 cases of SJS/TEN (22.6%) and 41 cases of DRESS (77.4%). The median patient age was 57.0 years. The patients with SJS/TEN were significantly older than those with DRESS (70.5 vs. 50.0 years, $P < 0.001$). DRESS patients were relatively evenly distributed across all age groups, while SJS/TEN patients were predominant among those 60 years or older. In 83.3% of patients, ATDs were prescribed for treatment of pulmonary tuberculosis. There were no significant differences in patient sex, type of tuberculosis, underlying allergic diseases, and comorbidities including diabetes mellitus, hypertension, liver disease, chronic kidney disease, rheumatic disease, infection, and malignancy according to the SCAR type (**Table 2**).

The median latent period was 27.0 days. The latent periods were significantly longer in patients with SJS/TEN than in patients with DRESS (50.0 vs. 21.0 days, $P = 0.036$). There was no difference in the duration of hospitalization according to the SCAR type in the ATD group. The rate of ICU admission was higher in patients with SJS/TEN (41.7% vs. 6.1%, $P = 0.010$).

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Table 1. Clinical characteristics of patients according to the causative drugs

Characteristics	Anti-tuberculosis drugs (n = 53)	Other drugs (n = 730)	*P* value
SCAR type			< 0.001
SJS/TEN	12 (22.6)	396 (54.2)	
DRESS	41 (77.4)	334 (45.8)	
Age (yr)	57.0 (21.0–86.0)	55.0 (0–95)	0.439
SJS/TEN	70.5 (42.0–86.0)	54.0 (0–94)	< 0.001
DRESS	50.0 (21.0–82.0)	55.0 (1–95)	0.178
Male	25 (47.2)	361 (49.5)	0.778
Allergic disease			
Asthma	2 (4.9)	17 (2.3)	0.507
Atopic dermatitis	1 (2.3)	7 (1.0)	0.810
Drug allergy	3 (8.8)	48 (6.6)	0.429
Other disease			
Diabetes mellitus	7 (15.6)	114 (15.6)	0.315
Hypertension	9 (20.0)	254 (34.8)	0.014
Liver disease	1 (2.2)	38 (5.2)	0.397
Chronic kidney disease	4 (9.3)	59 (8.1)	0.482
Rheumatic disease	2 (5.0)	48 (6.6)	0.455
Malignancy	5 (11.1)	61 (8.4)	0.915
Latent period (day)	27.0 (0–148.0)	14.0 (0–182.0)	0.002
Disease period (day)	29.0 (4.0–105.0)	20.0 (2.0–168.0)	0.003
Hospitalization period (day)	19.0 (1.0–85.0)	15.0 (0–228.0)	0.326
ICU admission	7 (15.6)	57 (7.8)	0.025
SJS/TEN	5 (41.7)	35 (8.8)	0.001
DRESS	2 (6.1)	22 (6.6)	0.313
Treatment			
IVIG	6 (11.3)	118 (16.2)	0.566
Systemic steroid	35 (66.0)	621 (85.1)	< 0.001
Clinical outcome			
Deaths (total)	5 (9.6)	46 (6.4)	0.339
SJS/TEN	4 (33.3)	32 (8.2)	0.011
DRESS	1 (2.5)	14 (4.2)	0.838

Values are expressed as number (%) or median with range.
SCAR, severe cutaneous adverse reaction; SJS, Stevens-Johnson syndrome; TEN, toxic epidermal necrolysis; DRESS, drug reaction with eosinophilia and systemic symptoms; ICU, intensive care unit; IVIG, intravenous immunoglobulin.

Treatments were classified into 4 groups: conservative care, corticosteroids, intravenous immunoglobulin (IVIG), and a combination of corticosteroids and IVIG. Of the 53 cases, 17 (32.7%) were managed with supportive care alone, all of which had DRESS. Thirty-five patients (66.0%) were treated with systemic corticosteroids. The systemic corticosteroid administration rate was significantly higher in patients with SJS/TEN than with DRESS (100% vs. 56.1%, $P = 0.019$). However, the duration of treatment and the mean daily dose were not significantly different between the 2 groups. Six patients were treated with IVIG, and the proportion of patients treated with IVIG was higher in patients with SJS/TEN than with DRESS (33.3% vs. 4.9%, $P = 0.019$). All patients who received IVIG also received steroids.

Most patients (86.5%) recovered without sequelae. The overall mortality rate was 9.6% in patients with ATD-induced SCARs. A significantly higher mortality rate was observed in patients with SJS/TEN than with DRESS (33.3% vs. 2.5%, $P = 0.019$).

The clinical features and laboratory results indicating systemic involvement are summarized in **Supplementary Table S1**. The prevalence rates of skin detachment and vesicle/bullae were significantly higher in the SJS/TEN group than in the DRESS group (75.0% vs. 7.3%, $P < 0.001$ and 50.0% vs. 7.3%, $P = 0.002$, respectively). The prevalence of hepatic involvement was significantly higher in patients with DRESS than with SJS/TEN (82.9% vs. 33.3%, $P = 0.007$).

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Table 2. Demographic and clinical characteristics

Characteristics	Total (n = 53)	SJS/TEN (n = 12)	DRESS (n = 41)	*P* value
Age (yr)	57.0 (21.0–86.0)	70.5 (42.0–86.0)	50.0 (21.0–82.0)	< 0.001
20–39	14 (26.4)	0	14 (34.1)	0.002
40–59	18 (34.0)	2 (16.7)	16 (39.0)	
≥ 60	21 (39.6)	10 (83.3)	11 (26.8)	
Male	25 (47.2)	7 (58.3)	18 (43.9)	0.378
Type of tuberculosis				0.086
Pulmonary	44 (83.0)	8 (66.7)	36 (87.8)	
Extra-pulmonary	9 (17.0)	4 (33.3)	5 (12.2)	
Allergic diseases				
Asthma	2 (4.9)	2 (20.0)	0	0.055
Atopic dermatitis	1 (2.3)	0	1 (2.3)	1.000
Drug allergy	3 (8.8)	0	3 (10.7)	1.000
Other diseases				
Diabetes mellitus	7 (15.6)	2 (20.0)	5 (14.3)	0.642
Hypertension	9 (20.0)	3 (30.0)	6 (17.1)	0.393
Liver disease	1 (2.2)	0	1 (2.9)	1.000
Chronic kidney disease	4 (9.3)	2 (20.0)	2 (6.1)	0.226
Rheumatic disease	2 (5.0)	1 (11.1)	1 (3.2)	0.404
Malignance	5 (11.1)	1 (10.0)	4 (11.4)	1.000
Latent period (day)	27.0 (0–148.0)	50.0 (8.0–148.0)	21.0 (0–110.0)	0.036
Disease period (day)	29.0 (4.0–105.0)	21.5 (4.0–72.0)	29.5 (5.0–105.0)	0.749
Hospitalization period (day)	19.0 (1.0–85.0)	16.0 (1.0–40.0)	21.0 (1.0–85.0)	0.198
ICU admission	7 (15.6)	5 (41.7)	2 (6.1)	0.010
Treatment				
IVIG	6 (11.3)	4 (33.3)	2 (4.9)	0.019
Systemic steroid	35 (66.0)	12 (100)	23 (56.1)	0.019
Clinical outcome				0.003
Recovery	45 (86.5)	7 (58.3)	38 (95.0)	
Sequela	2 (3.8)	1 (8.3)	1 (2.5)	
Death	5 (9.6)	4 (33.3)	1 (2.5)	

Values are expressed as number (%) or median with range.
SJS, Stevens-Johnson syndrome; TEN, toxic epidermal necrolysis; DRESS, drug reaction with eosinophilia and systemic symptoms; ICU, intensive care unit; IVIG, intravenous immunoglobulin.

We also analyzed data after subclassifying patients into 2 groups according to survival. The clinical features and laboratory results of the survival and mortality subgroups are summarized in **Supplementary Table S2**. Leukocyte and platelet levels were significantly lower in the mortality subgroup ($P = 0.037$ and $P = 0.002$, respectively). Heart rate and blood urea nitrogen were significantly higher in the mortality subgroup 7 days after admission ($P = 0.015$ and $P = 0.009$, respectively).

Culprit drugs of ATD-related SCARs

On average, 3 tuberculosis (TB) drugs were reported as causative drugs. The causal relationships were evaluated as "certain" in 11 cases, "probable" in 13 cases, and "possible" in 29 cases. When the assessing drug causality algorithm ALDEN was applied to SJS/TEN, the causal relationships were evaluated as "very probable" in 2 cases, "probable" in 4 cases, and "possible" in 6 cases.

According to data on the number of causative drugs reported by allergists, 13 cases were caused by a single drug, 8 cases by 2 drugs, 7 cases by 3 drugs, 23 cases by 4 drugs, and 2 cases by 5 drugs. Only 24.5% of the cases were reported to be a single causative agent. The number of causative agents did not differ according to clinical features. The ATD associated most often with SCAR cases was rifampin (75.5%), followed by isoniazid (62.3%), ethambutol (62.3%), pyrazinamide (52.8%), and quinolones (9.4%) (**Figure A**). There was no

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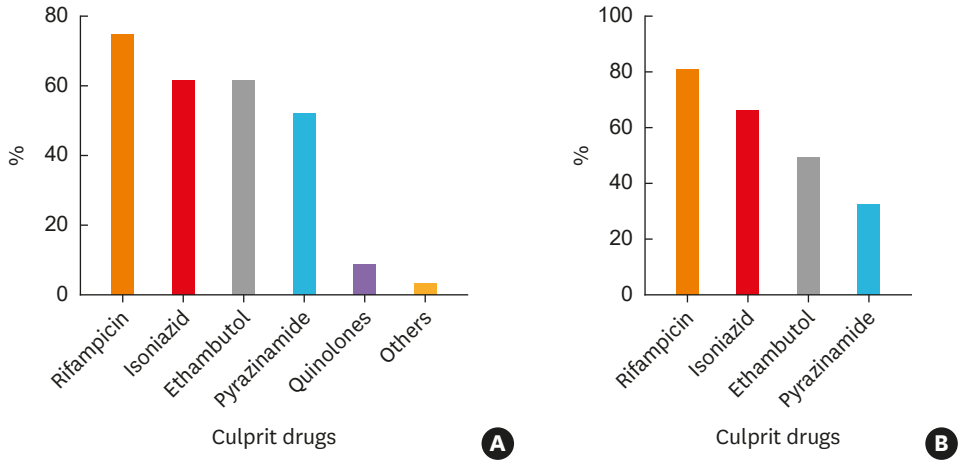

Figure. Percentages of culprit drugs (A) reported by allergist and (B) confirmed by drug challenge.

significant difference in the proportion of any specific ATD between patients with SJS/TEN and DRESS.

ATDs were challenged in 14 cases (26.4%), including 13 cases of DRESS (**Table 3**). The ATD associated most often with SCAR cases was rifampin (81.8%), followed by isoniazid (66.7%), ethambutol (50.0%), pyrazinamide (33.3%) (**Figure B**). While 8 patients (57.1%) had a single causative agent, 6 patients (42.9%) had reactions to 2 or more drugs. Five out of 10 patients who were challenged with rifampin and ethambutol had reactions to both of them.

DISCUSSION

This is the first study to evaluate the clinical characteristics, causative drugs, and outcomes of patients with ATD-induced SCARs and to compare the clinical differences between patients who developed SJS/TEN and those who developed DRESS. Several studies have reported ATD-associated DRESS[5,17,18]; however, few cases of ATD-associated SJS/TEN have been

Table 3. Cases of reintroduction of anti-tuberculosis drugs

Case	Age	Sex	Diagnosis	Culprit drugs	Reintroduction					
					R	I	E	P	Q	Others
1	77	M	DRESS	R, I, E, P	+	+	+	+	NA	
2	32	F	DRESS	R, E, P	+	NA	+	+	NA	
3	60	M	DRESS	R, I, E	+	+	+	U	NA	
4	36	F	DRESS	R, E	+	NA	+	NA	NA	
5	44	F	DRESS	R, I	+	+	–	U	NA	
6	59	M	DRESS	I, E	–	+	+	–	NA	
7	51	M	DRESS	P	NA	NA	NA	+	NA	
8	58	F	DRESS	R	+	–	–	–	NA	
9	70	F	DRESS	R	+	–	–	–	NA	
10	67	M	DRESS	R	+	U	U	U	NA	
11	52	M	DRESS	R	+	–	–	–	NA	
12	78	F	DRESS	I	–	+	–	–	NA	
13	65	M	TEN	I	U	+	U	U	NA	
14	33	M	DRESS	Q	NA	NA	NA	–	+	PROT-, CS-

R, rifampicin; I, isoniazid; E, ethambutol; P, pyrazinamide; Q, quinolones; M, male; F; female, DRESS, drug reaction with eosinophilia and systemic symptoms; NA, not applicable (nonculprit drug); –, no recurrence of clinical symptom; +, recurrence of clinical symptom; PROT, prothionamide; CS, cycloserine; U, unknown; TEN, toxic epidermal necrolysis.

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reported.[19] In this study, we report the clinical features and outcomes of 12 SJS/TEN cases. In addition, more than 40% of patients who were challenged with suspected drugs had reactions to more than 2 drugs. These results suggest the possibility of multiple drug hypersensitivity (MDH) to ATDs.

In the ATD group, the average latent period was 27 days. ATD-induced SCARs have a longer latent period than non-ATD-induced SCARs. The latent period in patients who developed DRESS in the present study was similar to those found in previous studies.[5,18] During the latent period and course of the disease, SCARs caused by ATDs are thought to slowly deteriorate and then gradually improve in the patients after ATD discontinuation compared to SCARs caused by other drugs. Clinical manifestations may vary according to causative drugs and underlying disease. Further studies are needed to determine whether these differences are characteristic of SCARs caused by ATDs.

In the present study, the mortality rate was significantly higher in patients with SJS/TEN compared to those with non-ATD-induced SCARs. A study by Hsu *et al.*[20] revealed that predictors of mortality in patients with SJS/TEN include increasing age, infections such as septicemia, pneumonia, and tuberculosis, number of chronic conditions, hematological malignancies, and renal failure. According to data released in 2015, the mortality rate of TB in Korea was 5.2 per 100,000 people, and although this rate is steadily decreasing, it remains higher than those in other countries.[1] The age of patients with ATD-induced SJS/TEN was very high in the present study compared to the SJS/TEN induced by different drugs in other studies.[10,21,22] Prognostic factors were not identified in the current study. However, high heart rate and blood urea nitrogen levels as well as low leukocyte and platelet counts were observed in the high mortality subgroup. Further studies are needed to investigate factors that determine the prognosis and mortality in patients with ATD-induced SCARs.

In this study, the median age of patients who developed SCARs was 57 years, with SJS/TEN patients being significantly older than DRESS patients. The median age of patients who developed DRESS was 50 years, which was younger than that of patients with DRESS in a previous French study (median age: 61 years).[5] Moreover, the incidence of SJS/TEN was high and the prognosis was poor in the elderly, indicating that older adults receiving ATDs should be observed more carefully. Clinical phenotypes did not differ according to patient sex in this study, which is inconsistent with the results of a previous French study in which women were found to be more likely to develop DRESS.[5] These discrepancies may be due to genetic or environmental differences between the study populations. Future extensive studies in Asian populations are warranted to resolve the discrepancies. Human immunodeficiency virus (HIV) coinfection contributes greatly to the global burden of tuberculosis. HIV co-infection promotes the susceptibility of people with HIV to TB disease by 20- to 30-fold and worsens disease severity.[23] A previous study documented that drug-related rashes were 100 times more common in HIV-infected patients than in the control patients.[24] However, our study did not include individuals with HIV.

Because of the nature of tuberculosis treatment, many ATDs should be administered concurrently. Therefore, it is often difficult to identify individual SCAR-inducing ATDs. Several drugs have been simultaneously identified as causative agents in the registry used in the present study. Of these, rifampin was the most frequent SCAR-inducing ATD, which is consistent with previous findings.[5]

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The reintroduction of drugs suspected of inducing SCARs is contraindicated. However, because of the nature of tuberculosis treatment, the lack of adequate therapeutic alternatives, and the risk/benefit balance, reintroduction can be justified in some cases.[5] A patch or intradermal test with delayed reading and lymphocyte transformation assays could be considered to be a method for identifying a causative ATD, but only a few data are available in the literature regarding the usefulness of these tests.[25,26] Oral provocation testing is the most accurate method for identifying causal drugs, but the risk of adverse effects in patients' health is high, and the method requires constant monitoring of patients, making it labor intensive. In the current study, 14 of the 53 subjects underwent drug challenge; of these patients, 1 had TEN. Rifampin was also found to be the most common causative drug in these tests.

MDH is a long-lasting drug hypersensitivity reaction to chemically unrelated drugs and is caused by extensive T-cell stimulation.[27] In previous studies, persistent T-cell activation accounted for by a subset of $CD4^+$ $CD25^{dim}$, $CD38^+$, and $PD\text{-}1^+$ T cells was found from MDH. This persistent stimulation could be related to subsequent development of further drug hypersensitivity to new drugs.[28] The prevalence of MDH ranges from 0.6% to 2.5% in patients with drug hypersensitivity. In SCAR patients, conversely, MDH is reported at a prevalence rate from 10% to 18%, especially with DRESS.[28] The suggested risk factors for MDH are DRESS, type of drug, high or recently increased drug dosages, combination therapy, and longer-lasting treatment.[27] Given the characteristics of tuberculosis treatment, patients with DRESS caused by ATDs are likely to be at high risk of MDH.

A few cases of MDH to ATDs have been previously reported.[29-31] In over 40% of the patients, multiple drugs also yielded positive results in the same subjects, which can be considered the potential for MDH to ATDs. This study is the first case series to report MDH to ATDs. In particular, 5 out of 10 patients who were challenged with rifampin and ethambutol had reactions to both of them.

To date, little has been known about cross-reactivity between ATDs and alternative treatments in MDH. As a limitation of registry research, this study did not include the results of studies on alternative treatments. Additional large-scale studies are needed. However, the possibility of a flare-up phenomenon playing a role in MDH to ATDs cannot be ruled out. Insufficient data are available regarding the optimal timing and dosing schedule of re-challenge. Recent studies have demonstrated the potential utility of enzyme-linked immunospot assay in measuring interferon γ release in patients with SCARs to identify causative drugs.[32-34] This method was not employed in this study due to limitations to registry research.

A few limitations to the present study should be addressed. Data availability was limited in some cases, with missing values in some patients. We could not analyze the SCORTEN scores or evaluate human herpesvirus 6 reactivation in the study participants. In addition, there exists the possibility of selection bias. Despite thorough checking and evaluation, we were unable to collect the detailed history of pre-existing diseases and concurrent medications. Although DRESS patients rarely have skin detachment, there were 2 patients with skin detachment during recovery and 4 people were identified to overlap vesicles. These patients were classified as DRESS patients based on the major lesion. This is also considered a limitation to registry research. The data on causative drugs were compiled based on registry data. Drug challenge tests were not conducted on all patients. Even though a drug challenge was conducted, it was not based on the unified induction test protocol. However, despite these limitations, this is the first large-scale study of ATD-induced SCARs in the Korean population.

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In conclusion, we described the clinical characteristics of ATD-associated SCARs and compared the clinical differences between SJS/TEN and DRESS cases. Compared to patients with DRESS, those with SJS/TEN were older and had a higher mortality rate. Although all ATDs carried the risk of inducing SCARs, rifampin was most frequently associated with the occurrence of SCARs. There were often hypersensitivity reactions to 2 or more drugs of ATDs as a result of drug challenge. The possibility of MDH to ATDs should be considered in clinical practice. Further studies are warranted to clarify causative agents and risk factors of ATD-associated SCARs.

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SUPPLEMENTARY MATERIALS

Supplementary Table S1

Clinical manifestations and laboratory findings

Click here to view

Supplementary Table S2

Clinical characteristics in survival and fatal cases

Click here to view

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