Kim et al. World Allergy Organization Journal (2023) 16:100738
http://doi.org/10.1016/j.waojou.2022.100738

WORLD ALLERGY ORGANIZATION JOURNAL

Open Access

Clinical aspects of severe cutaneous adverse reactions caused by beta-lactam antibiotics: A study from the Korea SCAR registry

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ABSTRACT

Background: Although beta-lactams are 1 of the major causative agents of severe cutaneous adverse reactions (SCAR), their epidemiology and clinical aspects have been poorly studied. This study aimed to investigate the characteristics of SCAR caused by beta-lactams in the Korean SCAR registry.

Methods: We retrospectively analyzed beta-lactam-induced SCAR cases collected from 28 tertiary university hospitals in Korea between 2010 and 2015. The SCAR phenotypes included Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), SJS-TEN overlap, and drug reaction with eosinophilia and systemic symptoms (DRESS). Beta-lactams were classified according to their chemical structures: penicillins, cephalosporins, and carbapenems. The causative beta-lactams, clinical and laboratory features, treatments, and outcomes were evaluated.

Results: Among the 275 antibiotic-induced SCAR cases, 170 patients developed SCAR induced by beta-lactams. Beta-lactam antibiotic-induced SCAR showed more frequent SJS/TEN compared to SCAR induced by non-beta-lactam antibiotics (SJS/TEN/SJS-TEN overlap/DRESS: 36.5/11.2/5.9/46.5% vs. 23.8/10.5/2.9/62.9%, $P = 0.049$). Cephalosporin was the most common culprit drug. Particularly, 91 and 79 patients presented with SJS/TEN and DRESS, respectively. The odds ratio (OR) for poor prognosis, such as sequelae and death, was significantly increased in subjects with SJS-TEN overlap and TEN and carbapenem as culprit drug in the multivariate analysis (OR, 35.61; $P = 0.016$, OR, 28.07; $P = 0.006$, OR 30.46; $P = 0.027$).

Conclusion: Among antibiotic-induced SCAR, clinical features were different depending on whether the culprit drug was a beta-lactam antibiotic or SCAR type. The poor prognosis was related to SJS-TEN overlap, TEN type, and carbapenem as the culprit drug.

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http://doi.org/10.1016/j.waojou.2022.100738
Received 1 May 2022; Received in revised from 29 November 2022; Accepted 9 December 2022
Online publication date 12 January 2023

Keywords: Antibacterial agents, Beta-lactams, Drug hypersensitivity syndrome, Stevens-Johnson syndrome, Toxic epidermal necrolysis

INTRODUCTION

Drug hypersensitivity reactions are common obstacles that interfere with patient care. These reactions are caused by immunological mechanisms that occur in approximately 2.3–3.6 cases per 1000 patients.[1] Although most drug eruptions are mild maculopapular exanthema, they also include severe phenotypes, such as Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), and drug-induced hypersensitivity syndrome (DIHS)/drug reaction with eosinophilia and systemic symptoms (DRESS), termed severe cutaneous adverse drug reactions (SCAR).[2] SCAR are known to develop in 2% of hospitalized patients, 2–7 cases/million per year for SJS/TEN and 1/1000–1/10,000 cases for DIHS.[2] Overall, this is an extremely rare but serious problem encountered during treatment.[2]

The clinical features of SCAR are diverse. They may have various types of skin involvement with characteristic mucocutaneous involvement. In contrast, DIHS/DRESS has almost no skin detachment and is mainly accompanied by internal organ involvement and hematological abnormalities, such as fever, hepatitis, and eosinophilia. However, there can be overlap in some of the clinical features of SJS/TEN and DRESS, and there is no clear boundary.[2] There have been several reports of complications caused by SCAR.[2] In the case of SJS/TEN, there may be skin scarring and ophthalmic, genitourinary, and respiratory complications, and in the case of DIHS, end organ failure, and autoimmune disease may develop.[2] It has been shown that certain human leukocyte antigen types are associated with an increased risk of SCAR with certain drugs.[3–5] However, there are insufficient studies on other factors related to SCAR occurrence and prognosis.

Beta-lactam antibiotics, including penicillins and cephalosporins, are the most commonly used antibiotics for infectious diseases in clinical practice and the most common cause of drug allergy.[6] Nevertheless, few studies have been conducted on beta-lactam antibiotic-induced SCAR; therefore, we aimed to study the clinical characteristics and factors related to poor prognosis of SCAR caused by beta-lactam antibiotics.

METHODS

Study subjects and resources

This study was based on data collected from the Korean SCAR registry, these data were described in previous studies.[7,8] The Korean SCAR registry is web-based and originated from the Regional Pharmacovigilance Center (RPVC) of the Korean Food and Drug Administration (KFDA). Currently, 36 tertiary hospitals are participating, and at least 1 allergist reviews cases at each institution participating in this registry.[9] Briefly, the Korean SCAR registry retrospectively collected drug allergy data from 36 tertiary hospitals nationwide from 2010 to 2015. Each case was registered after reviewing medical records by 2 physicians, including at least 1 allergist, and the definition of SCAR was based on the same criteria as in previous studies. The causal relationship between the suspected drug and SCAR was evaluated using the World Health Organization–Uppsala Monitoring Center (WHO-UMC) criteria.[10] The WHO-UMC criteria is based on 5 items: plausible time relationship between drug intake and events, cannot be explained by disease or other drugs, response to withdrawal plausible drug, event definitive pharmacologically or phenomenologically, and rechallenge satisfactory. Causalities were then classified into 4 stages: certain, probable, possible, and unlikely (Supplementary Table 1).[11] Cases with possible or higher levels of causality were included.

If more than 2 possible causal drugs were used simultaneously, all suspected drugs assigned as culprit drugs based on expert judgment. Demographic information, hospitalization status, vital signs, laboratory tests, medical history, drug history, and clinical course were collected from a review of medical records.

Institutional Review Board (IRB) approval was obtained from each research participating institution (IRB approval number of the representative institution, Seoul National University Bundang Hospital is B-1802-450-401.).

Evaluation of clinical data on beta-lactam SCAR

The cases of SCAR caused by antibiotics were divided into cases of beta-lactam antibiotic-induced SCAR and cases of non-beta-lactam antibiotic-induced SCAR. Within beta-lactam antibiotic-induced SCAR cases, penicillins, cephalosporins, and carbapenems-were classified according to the culprit drug classifications. We evaluated whether there was a difference in the clinical characteristics and prognosis according to the beta-lactam or non-beta-lactam antibiotics and SCAR types.

Statistical analysis

Statistical analysis was performed using SPSS software (version 22.0; SPSS, IBM Inc., Chicago, IL, USA). Continuous variables were presented as means ± standard deviation or median interquartile range and analyzed using the *t*-test or Mann-Whitney *U* test. Categorical variables were presented as numbers or percentages and were analyzed using Pearson's χ^2 test or Fisher's exact test. A *P*-value <0.05 indicated statistical significance. Binary logistic regression analysis was performed to find factors related to the prognosis of SCAR, and statistically significant factors in univariate analysis and factors judged to be clinically important, such as age and sex, were adjusted.

RESULTS

Demographic and clinical characteristics

Data of 275 patients with SCAR due to antibiotics were extracted, of which 170 were classified as SCAR due to beta-lactam antibiotics and 105 as SCAR due to non-beta-lactam antibiotics (Table 1, Fig. 1A). Patients with beta-lactam antibiotic-induced SCAR had a mean age of 50.8 years, and 55.9% were male. Hypertension was the most common comorbidity, followed by diabetes mellitus, cancer, chronic kidney disease, and chronic liver disease (Table 1). On average, 72.4% of the body surface area (BSA) was affected. Mucosal involvement was detected in 61.6% of patients, fever in 62.3%, and lymphadenitis in 14.9%. The median disease duration was 18.0 (Interquartile range, IQR 13.0–27.0) days, the administration duration of culprit drugs was 8.0 (IQR 3.0–17.0) days, latent period which is the period form the antibiotics intake to the onset of reaction was 9.0 (IQR 1.0–22.0) days, and admission duration was 17.0 (IQR 10.0–35.5) days. In 14.6% of the patients, there was a history of exposure to the suspected drug. As treatment, 78.3% received systemic corticosteroids, 19.0% received intravenous immunoglobulin (IVIG), and 4.7% received intensive care. The mean SCORTEN score was 1.0 on day 1 and 1.7 on day 7. However, 85.7% of patients recovered without sequelae, sequelae remained in 7.7%, and 6.5% of patients died.

Compared with patients with non-beta-lactam antibiotic-induced SCAR, patients with beta-lactam antibiotic-induced SCAR had a lower body mass index (BMI) (21.6 ± 3.3 vs. 22.8 ± 4.0, $P = 0.022$), and fewer allergic diseases (10.0% vs. 20.5%, $P = 0.032$); SJS/TEN was more common, and DRESS was less in SCAR type (SJS/TEN/SJS-TEN overlap/DRESS 36.5/11.2/5.9/46.5% vs. 23.8/10.5/2.9/62.9%, $P = 0.049$). The duration of drug administration after symptom onset was shorter in beta-lactam antibiotic-induced SCAR (3.0 vs. 7.0 days, $P = 0.006$).

Among the 170 patients with beta-lactam antibiotic-induced SCAR, the most common suspected drug class was cephalosporins, especially third-generation cephalosporins, and the second most common suspected class was penicillins, especially aminopenicillins (Fig. 1B). SJS/TEN was more frequent in penicillins and DRESS was more frequent in carbapenems, but the differences were not statistically significant (Fig. 1C).

Comparison according to SCAR phenotype

In the analysis of SCAR types, patients with DRESS had the highest BMI (SJS/SJS-TEN overlap/TEN/DRESS 21.0/21.6/20.2/22.6, $P = 0.021$), and other allergic diseases were most frequently accompanied by TEN (26.7%, $P = 0.042$) (Table 2). Mucosal involvement was lowest in patients with DRESS (SJS/SJS-TEN overlap/TEN/DRESS 86.8, 88.0, 92.5, 21.7, $P < 0.001$), and BSA was highest in patients with TEN (48.3%, $P < 0.001$). As expected, subjects with DRESS more frequently

	Total	Non-beta-lactam	Beta-lactam	*P*-value
Number of cases	275	105 (38.2%)	170 (61.8%)	
Age	53.3 ± 20.6	54.7 ± 21.5	50.8 ± 22.1	0.158
Male %	146 (53.1%)	51 (48.6%)	95 (55.9%)	0.264
BMI	22.6 ± 3.7	22.8 ± 4.0	21.6 ± 3.3	**0.022**
Smoking history (Non-/Ex-/ Current smoker)	177/20/23 (80.5/9.1/10.5%)	77/6/7 (85.6/6.7/7.8%)	100/14/16 (76.9/10.8/12.3%)	0.298
	33/238 (13.9%)	18/88 (20.5%)	15/150 (10.0%)	**0.032**
History of drug allergy	18/191 (9.4%)	11/76 (14.5%)	7/108 (6.1%)	0.075
Comorbidities				
Diabetes mellitus	44/246 (17.9%)	15/93 (16.1%)	29/153 (19.0%)	0.611
Hypertension	81/245 (33.1%)	31/93 (33.3%)	50/152 (32.9%)	1.000
Chronic liver disease	12/236 (5.1%)	4/92 (4.3%)	8/144 (5.6%)	0.770
Chronic kidney disease	16/229 (7.0%)	6/89 (6.7%)	10/140 (7.1%)	1.000
Cancer	24/229 (10.5%)	6/87 (6.9%)	18/142 (12.7%)	0.189
Admission route				
SCAR onset during hospitalization (%)	71/273 (26.0%)	25 (23.8%)	46 (27.4%)	0.572
Via OPD (%)	76/273 (27.8%)	34 (32.4%)	42 (25.0%)	0.212
Via ER (%)	126/273 (46.2%)	46 (43.8%)	80 (47.6%)	0.618
SCAR type (SJS/TEN/SJS-TEN overlap/ DRESS or DHS)	87/30/13/145 (31.6/10.9/4.7/ 52.7%)	25/11/3/66 (23.8/ 10.5/2.9/62.9%)	62/19/10/79 (36.5/11.2/5.9/ 46.5%)	**0.049**
Presenting symptoms				
Skin involvement, BSA (%)	74.2 ± 30.2	76.9 ± 29.7	72.4 ± 30.5	0.246
Mucosal involvement	115/204 (56.4%)	38/79 (48.1%)	77/125 (61.6%)	0.062
Fever	173/261 (66.3%)	74/102 (72.5%)	99/159 (62.3%)	0.107
Lymphadenitis	21/119 (17.6%)	10/45 (22.2%)	11/74 (14.9%)	0.330
Highest body temperature	39.0 ± 0.7	39.1 ± 0.7	39.0 ± 0.8	0.432
Duration of fever	6.2 ± 7.2	7.3 ± 8.8	5.3 ± 5.5	0.093
Highest WBC count	18653.0 ± 27901.0	24258.2 ± 42531.7	14847.0 ± 7506.7	0.110
Highest eosinophil count	1493.9 ± 2083.8	1612.3 ± 2023.0	1408.7 ± 2131.2	0.501
Highest creatinine level	2.0 ± 2.2	2.3 ± 2.6	1.7 ± 1.8	0.130
Highest ALT level	211.4 ± 286.1	241.7 ± 300.2	190.5 ± 275.1	0.205
Administration of culprit (days)	11.0 (IQR 4.0–21.0)	17.0 (IQR 7.0–27.0)	8.0 (IQR 3.0–17.0)	0.140
Duration of drug administration after symptom onset (days)	3.0 (IQR 2.0–5.0)	4.0 (IQR 2.0–9.0)	2.0 (IQR 1.0–4.0)	**0.006**
Latent period	11.0 (IQR 2.0–23.0)	13.0 (IQR 6.0–26.0)	9.0 (IQR 1.0–22.0)	0.314
Disease duration (days)	20.0 (IQR 14.0–30.0)	22.0 (IQR 14.0–34.0)	18.0 (IQR 130–27.0)	0.640
Admission duration (days)	18.0 (IQR 11.0–33.0)	18.0 (IQR 11.0–32.5)	17.0 (IQR 10.0–35.5)	0.673

(continued)

	Total	Non-beta-lactam	Beta-lactam	*P*-value
SJS	13.0 (IQR 7.75–26.25)	14.0 (IQR 6.5–28.0)	13.0 (IQR 8.0–20.0)	0.904
SJS/TEN Overlap	26.0 (IQR 18.0–39.0)	27.0 (IQR 26.0–27.0)	25.0 (IQR 17.25–39.0)	0.346
TEN	32.0 (IQR 14.0–51.5)	26.0 (IQR 16.0–40.0)	34.5 (IQR 13.0–56.0)	0.715
DRESS or DHS	18.0 (IQR 11.0–37.0)	18.0 (IQR 11.75–32.25)	19.0 (IQR 11.0–39.0)	0.912
Past exposure to culprit drug	16/144 (11.1%)	4/62 (6.5%)	12/82 (14.6%)	0.180
Treatment				
Systemic steroid	216/268 (80.6%)	86/102 (84.3%)	130/166 (78.3%)	0.267
IVIG	46/250 (18.4%)	16/92 (17.4%)	30/158 (19.0%)	0.866
Other immunosuppressant	5/248 (2.0%)	0/91 (0.0%)	5/157 (3.2%)	0.161
ICU care	13/275 (4.7%)	5/105 (4.8%)	8/170 (4.7%)	1.000
SCORTEN Day 1 (total 7)	1.0 ± 0.9	0.9 ± 1.0	1.0 ± 0.8	0.681
SCORTEN Day 7 (total 7)		1.8 ± 0.9	1.7 ± 1.0	0.843
Prognosis (%)				0.588
Improved	228/272 (83.8%)	84/104 (80.8%)	144/168 (85.7%)	
With sequelae	24/272 (8.8%)	11/104 (10.6%)	13/168 (7.7%)	
Death (%)	20/272 (7.4%)	9/104 (8.75)	11/168 (6.5%)	

Table 1. (Continued) Demographic and clinical characteristics of antibiotics-induced SCAR patients. *SCAR, severe cutaneous adverse reaction; BMI, body mass index; OPD, out-patient department; ER, emergency room; 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; DHS, drug hypersensitivity syndrome; BSA, body surface area; WBC, white blood cells; Cr, creatinine; ALT, alkaline phosphatase; IQR, Interquartile range; IVIG, intravenous immunoglobulin; ICU, intensive care unit; SCORTEN, SCORe of Toxic Epidermal Necrosis*

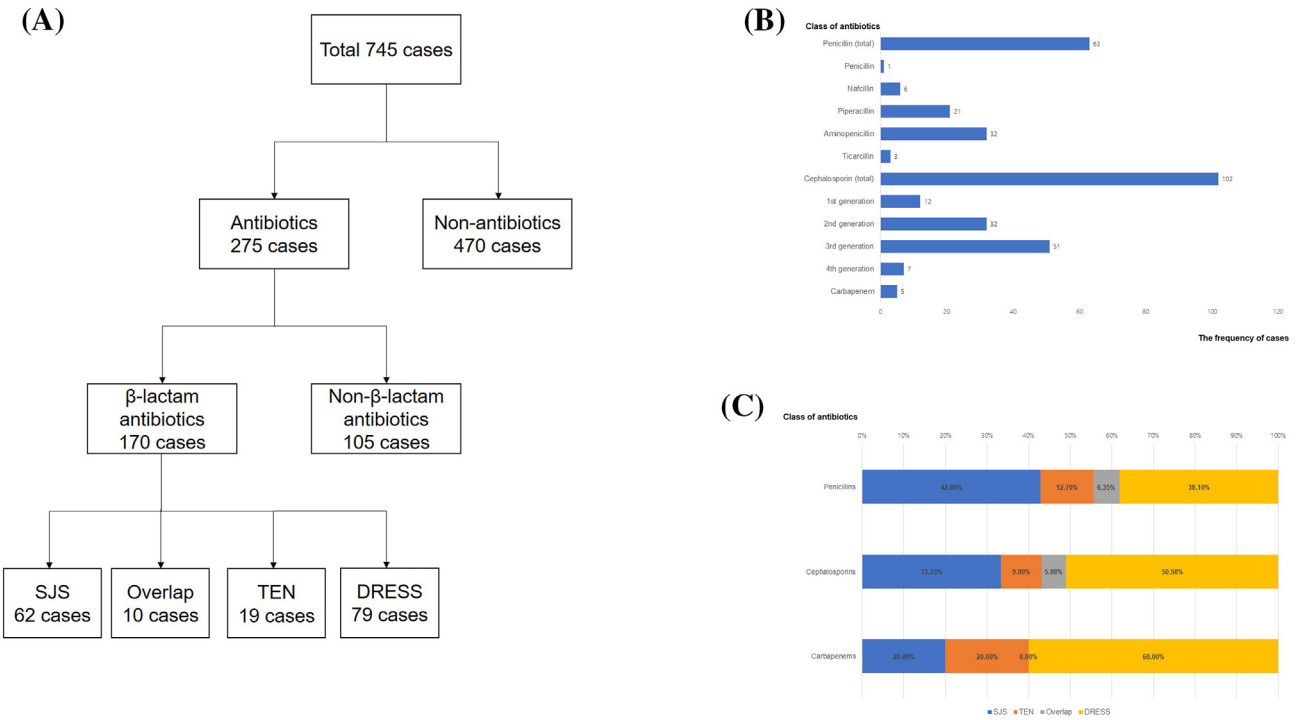

Fig. 1 The flowchart of case classification (A), distribution of subjects (B) and the proportions of SCAR types (C) according to culprit beta-lactam antibiotic class

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http://doi.org/10.1016/j.waojou.2022.100738

	SJS (n = 62)	Overlap (n = 10)	TEN (n = 19)	DRESS (n = 79)	*P*-value
Age (median, year)	46.1 ± 25.4	53.3 ± 24.7	52.1 ± 25.2	53.9 ± 17.7	0.479
Sex (% of males)	59.7	50.0	57.9	53.2	0.860
BMI (kg/m^2)	21.0 ± 3.3	21.6 ± 2.6	20.2 ± 4.9	22.6 ± 2.7	**0.021**
Other allergic disease (%)	3.8	0.0	26.7	12.5	0.042
Other drug hypersensitivity (%)	4.8	0.0	9.1	7.5	0.856
Comorbidities					
Chronic kidney disease	6.7	11.5	14.3	10.0	0.190
Chronic liver disease	5.9	0.0	2.7	6.3	0.476
Diabetes mellitus	14.1	20.7	15.4	19.3	0.370
Hypertension	35.1	46.9	38.7	36.6	0.613
Cancer	7.3	3.3	13.9	11.4	0.164
Presenting symptoms					
Mucosal involvement (%)	86.8	88.0	92.5	21.7	**< 0.001**
Involved BSA (%)	11.0 ± 28.7	19.9 ± 12.5	48.3 ± 28.7	14.1 ± 32.6	**< 0.001**
Fever (%)	48.0	56.3	63.6	67.7	**< 0.001**
Lymphadenitis (%)	3.1	6.7	9.3	28.3	**< 0.001**
Highest body temperature	38.9 ± 0.7	38.9 ± 0.6	39.1 ± 0.8	39.0 ± 0.7	0.231
Duration of fever (days)	3.9 ± 4.1	5.1 ± 4.3	9.2 ± 10.6	5.4 ± 6.2	**< 0.001**
Highest WBC count	13494.2 ± 7079.5	12098.8 ± 6570.4	14645.7 ± 7224.6	20165.7 ± 24518.5	**< 0.001**
Highest eosinophil count	868.4 ± 1462.1	797.7 ± 1175.4	894.7 ± 1906.9	2376.7 ± 3513.1	**< 0.001**
Highest serum Cr (mg/mL)	1.4 ± 1.2	2.4 ± 2.0	2.2 ± 2.0	2.2 ± 2.3	0.001
Highest serum ALT (IU/L)	172.7 ± 272.6	110.7 ± 116.3	197.1 ± 324.5	320.1 ± 506.8	**< 0.001**
Culprit drugs					0.600
Penicillins	27 (42.9%)	4 (6.3%)	8 (12.7%)	24 (38.1%)	
Cephalosporins	31 (33.3%)	6 (5.9%)	10 (9.8%)	52 (51.0%)	
Carbapenems	1 (20.0%)	0 (0.0%)	1 (20.0%)	3 (60.0%)	
Administration of culprit (days)	19.0 ± 30.1	4.9 ± 3.6	4.0 ± 4.2	18.6 ± 14.3	0.268
Duration of drug administration after symptom	6.7 ± 9.1	3.3 ± 2.4	8.0 ± 12.3	14.6 ± 80.0	**0.041**
Latent period (days)	17.8 ± 25.8	18.7 ± 28.7	18.8 ± 28.2	24.7 ± 23.8	**< 0.001**

Disease duration (days)	18.9 ± 11.0	40.4 ± 38.7	27.9 ± 12.9	27.6 ± 28.9	**0.011**
Admission duration (days)	15.7 ± 12.6	25.5 ± 17.5	33.2 ± 25.4	24.5 ± 26.7	**< 0.001**
Previous exposure to culprit (%)	9.9	31.3	13.0	9.5	0.075
Treatment					
Systemic steroid (%)	93.2	100.0	94.9	77.1	**< 0.001**
IVIG (%)	15.7	38.2	51.9	8.0	**< 0.001**
Other immunosuppressant	5.7	2.9	6.8	2.1	**0.054**
ICU care	4.6	17.6	26.3	6.3	**< 0.001**
SCORTEN Day 1 (total 7)	0.9 ± 0.8	1.6 ± 0.7	1.4 ± 0.9	0.9 ± 0.8	0.010
SCORTEN Day 7 (total 7)	1.6 ± 1.0	1.2 ± 0.6	2.2 ± 1.2	1.8 ± 0.9	**0.017**
SCORTEN Day 1 (% of ≥ 2)	23.2	28.6	36.6	24.1	0.092
SCORTEN Day 7 (% of ≥ 2)	51.3	68.6	76.8	62.0	**< 0.001**
Prognosis (%)					**< 0.001**
Improved	90.2	77.8	47.4	92.4	
With sequelae	6.6	22.2	26.3	2.5	
Death	3.3	0.0	26.3	5.1	

Table 2. Demographics and clinical presentations of beta-lactam antibiotics-induced SCARs according to phenotypes. *SCAR, severe cutaneous adverse reaction; BMI, body mass index; OPD, out-patient department; ER, emergency room; 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; DHS, drug hypersensitivity syndrome; BSA, body surface area; WBC, white blood cells; Cr, creatinine; ALT, alkaline phosphatase; IVIG, intravenous immunoglobulin; ICU, intensive care unit; SCORTEN, SCORe of Toxic Epidermal Necrosis*

showed fever, lymphadenitis and higher white blood cell (WBC) count, eosinophil count, and alanine aminotransferase (ALT) levels than those with other SCAR phenotypes. Conversely, the duration of fever was longest in patients with TEN, and serum creatinine (Cr) level was highest in patients with SJS-TEN overlap. The duration of drug administration even after symptom onset and latent period were longest in patients with DRESS as 14.6 days ($P < 0.041$) and 24.7 days ($P < 0.001$), respectively. The disease duration and hospitalization days were longer in patients with SJS-TEN overlap and TEN, at 40.4 days ($P < 0.011$) and 33.2 days ($P < 0.001$), respectively. Systemic corticosteroids were used more frequently in patients with SJS/TEN than in those with DRESS (SJS/SJS-TEN overlap/TEN/DRESS 93.2/100.0/94.9/77.1, $P < 0.001$), and IVIG was administered to 51.9% of patients with TEN ($P < 0.001$). Although the SCORTEN score on day 1 was highest in patients with SJS-TEN overlap (1.6 ± 0.7 [$P = 0.010$]), the SCORTEN score on day 7 was highest in patients with TEN (2.2 ± 1.2 [$P = 0.017$]), and the proportion of patients with a score of ≥2 on day 7 was also highest in patients with TEN (SJS/SJS-TEN overlap/TEN/DRESS 51.3, 68.6, 76.8, 62.0, $P < 0.001$). The most favorable prognosis was in patients with DRESS, with 92.4% of recovered patients and the worst prognosis was in patients with TEN, with 26.3% of the complications or death ($P < 0.001$). SCAR types and prognosis according to WHO-UMC causality evaluation was provided in Supplementary Table 2.

Factors related with prognosis

Regarding the factors related to prognosis, 28.7% of fully recovered patients developed SCAR during hospitalization, whereas no patient with sequelae developed SCAR during hospitalization ($P = 0.021$). DRESS was more frequent in patients with full recovery; TEN and SJS-TEN overlap were more frequent in patients with sequelae (SJS/TEN/SJS-TEN overlap/DRESS 38.2,6.3,4.9,50.7% vs.30.8,38.5,15.4,15.4%, $P = 0.001$) (Table 3). Moreover, the latent period was shorter (16.4 ± 23.6vs.4.9 ± 7.3, $P = 0.016$), and the rates of IVIG use and ICU care were higher in patients with sequelae (12.7%vs.41.7%, $P = 0.019$, 1.5% vs.33.3%, $P < 0.001$).

In patients with mortality, the amount of cigarette consumption was lower (3.8 ± 9.9% vs. 0.0 ± 0.0, $P < 0.001$), TEN was more frequent SCAR types (SJS/TEN/SJS-TEN overlap/DRESS 37.6/8.9/5.7/47.8% vs. 18.2/45.5/0.0/36.4%, $P = 0.015$), and the involved skin area was broader than in patients who survived (71.4 ± 31.0 vs. 87.5 ± 19.9, $P = 0.036$). Moreover, administration days of culprit drug were shorter (17.8 ± 21.2 vs. 5.9 ± 5.0, $P = 0.042$), and the rates of IVIG use and ICU care were higher (15.1% vs. 80.0%, $P < 0.001$, 4.1% vs. 45.5%, $P < 0.001$). Finally, a higher SCORTEN score on day 7 was associated with increased mortality (1.7 ± 0.9 vs. 2.9 ± 1.2, $P < 0.001$) (Table 3).

When the risk factors for poor prognosis leading to sequelae or death were analyzed, a higher SJS-TEN overlap and TEN, serum Cr level, and SCORTEN score on day 7 and, if carbapenems were the causative agents, a higher odds ratio for poor prognosis was observed in the univariate analysis (Table 4). However, in the multivariate analysis, the statistical significance of other factors disappeared, and the odds ratio of poor prognosis remained significant with SJS-TEN overlap/and TEN and was also significant when carbapenems were the causative agents.

DISCUSSION

In this study, there was a clinical difference between beta-lactam antibiotic-induced SCAR and non-beta-lactam antibiotic-induced SCAR. SJS/TEN was more common than DRESS in patients with beta-lactam antibiotic-induced SCAR, and the number of culprit drug administration days was shorter. Moreover, among patients with beta-lactam antibiotic-induced SCAR, different clinical features were observed according to the SCAR type. Patients with DRESS showed a higher BMI, higher frequency of fever and lymphadenitis as presenting symptoms, more elevated WBC count, eosinophil count, and ALT level, and longer duration of drug administration after symptoms and latent periods. Patients with TEN were more commonly accompanied by other allergic diseases and showed larger involved BSA, longer duration of fever and admission duration, higher proportion of IVIG use, higher SCORTEN score on day 7, and a

	Survival				Mortality	*P*-value
	Full recovery	Sequelae	*P*-value			
Number of cases	144 (91.7%)	13 (8.3%)		157 (93.5%)	11 (6.5%)	
Age	50.6 ± 22.3	45.7 ± 19.0	0.447	50.2 ± 22.0	59.6 ± 24.3	0.173
Male %	80/144 (55.6%)	6/13 (46.2%)	0.570	86/157 (54.8%)	8/11 (72.7%)	0.350
	21.9 ± 3.3	20.5 ± 2.8	0.177	21.8 ± 3.3	19.7 ± 3.6	0.053
Smoking history (Non-/Ex-/Current smoker)	15/12/83 (13.6/10.9/75.5%)	1/0/10 (9.1/0.0/90.9%)	0.740	16/12/93 (13.2/9.9/76.9%)	0/2/6 (0.0/25.0/75.0%)	0.195
Smoking history (pack-year)	4.0 ± 10.2	1.8 ± 6.0	0.483	3.8 ± 9.9	0.0 ± 0.0	<0.001
Allergic disease	12/126 (9.5%)	0/12 (0.0%)	0.600	12/138 (8.7%)	3/10 (30.0%)	0.066
History of drug allergy	6/97 (6.2%)	0/9 (0.0%)	1.000	6/106 (5.7%)	1/7 (14.3%)	0.369
Comorbidities						
Diabetes mellitus	24/130 (18.5%)	1/12 (8.3%)	0.692	25/142 (17.6%)	4/10 (40.0%)	0.098
Hypertension	42/129 (32.6%)	3/12 (25.0%)	0.752	45/141 (31.9%)	5/10 (50.0%)	0.300
Chronic liver disease	8/121 (6.6%)	0/12 (0.0%)	1.000	8/133 (6.0%)	0/10 (0.0%)	0.650
Chronic kidney disease	6/117 (5.1%)	1/12 (8.3%)	0.504	7/129 (5.4%)	2/9 (22.2%)	0.107
Cancer	14/119 (11.8%)	1/12 (8.3%)	1.000	15/131 (11.5%)	3/10 (30.0%)	0.118
Admission route						
SCAR onset during hospitalization (%)	41/143 (28.7%)	0/13 (0.0%)	0.021	41/156 (26.3%)	5/11 (45.5%)	0.177
OPD (%)	34/143 (23.8%)	5/13 (38.5%)	0.313	39/156 (25.0%)	3/11 (27.3%)	1.000
ER (%)	68/143 (47.6%)	8/13 (61.5%)	0.394	76/156 (48.7%)	3/11 (27.3%)	0.219
SCAR type (SJS/TEN/SJS-TEN overlap/DRESS or DHS)	55/9/7/73 (38.2/6.3/4.9/50.7%)	4/5/2/2 (30.8/38.5/15.4/15.4%)	0.001	59/14/9/75 (37.6/8.9/5.7/47.8%)	2/5/0/4 (18.2/45.5/0.0/36.4%)	0.015

(continued)

	Survival				Mortality	*P*-value
	Full recovery	Sequelae	*P*-value			
Presenting symptoms						
Skin involvement	70.4 ± 31.3	81.8 ± 26.7	0.206	71.4 ± 31.0	87.5 ± 19.9	0.036
Mucosal involvement	62/105 (59.0%)	10/12 (83.3%)	0.126	72/117 (61.5%)	4/7 (57.1%)	1.000
Fever	81/135 (60.0%)	7/12 (58.3%)	1.000	88/147 (59.9%)	10/11 (90.9%)	0.053
Lymphadenitis	9/61 (14.8%)	1/8 (12.5%)	1.000	10/69 (14.5%)	1/4 (25.0%)	0.487
SCORTEN	1.0 ± 0.8	1.2 ± 0.7	0.396	1.0 ± 0.8	1.4 ± 0.9	0.127
Highest body temperature	38.9 ± 0.7	39.5 ± 0.8	0.061	39.0 ± 0.7	39.0 ± 1.1	0.958
Duration of fever	5.0 ± 5.0	4.0 ± 2.2	0.651	5.0 ± 4.9	9.0 ± 10.6	0.355
Highest WBC count	14426.2 ± 7051.0	10865.0 ± 3997.8	0.322	18872.4 ± 27816.1	21957.1 ± 23487.1	0.775
Highest eosinophil count	1456.6 ± 2208.1	709.5 ± 711.7	0.503	1428.9 ± 2174.3	1044.0 ± 1144.9	0.669
Highest creatinine level	1.6 ± 1.5	2.3 ± 3.0	0.573	1.6 ± 1.6	2.9 ± 2.9	0.244
Highest ALT level	190.7 ± 283.0	157.6 ± 199.5	0.761	188.7 ± 278.2	219.6 ± 235.0	0.775
Administration of culprit (days)	18.9 ± 21.9	7.0 ± 7.5	0.133	17.8 ± 21.2	5.9 ± 5.0	0.042
Duration of drug administration after symptom onset (days)	3.17 ± 2.6	2.6 ± 2.1	0.641	3.1 ± 2.3	2.3 ± 1.4	0.407
Latent period (days)	16.4 ± 23.6	4.9 ± 7.3	0.016	15.4 ± 22.9	14.3 ± 19.8	0.873
Disease duration (days)	24.4 ± 22.1	30.6 ± 28.2	0.348	25.0 ± 22.6	40.2 ± 49.5	0.334
Admission duration (days)	26.8 ± 30.3	27.2 ± 29.1	0.961	26.8 ± 30.1	48.3 ± 50.6	0.193
Past exposure to culprit drug	8/68 (11.8%)	1/7 (14.3%)	1.000	9/75 (12.0%)	3/7 (42.9%)	0.061
Treatment						
Systemic steroid	107/142 (75.4%)	12/12 (100%)	0.069	119/154 (77.3%)	9/10 (90.0%)	0.693
Duration of steroid use (days)						
Total dose of steroid (mg)						
IVIG	17/134 (12.7%)	5/12 (41.7%)	0.019	22/146 (15.1%)	8/10 (80.0%)	<0.001

Other immunosuppressant	4/134 (3.0%)	1/12 (8.3%)	0.353	5/146 (3.4%)	0/9 (0.0%)	1.000
ICU care	2/134 (1.5%)	4/12 (33.3%)	<0.001	6/146 (4.1%)	5/11 (45.5%)	<0.001
SCORTEN Day 1 (total 7)	0.9 ± 0.8	1.2 ± 0.7	0.396	1.0 ± 0.8	1.4 ± 0.9	0.127
SCORTEN Day 7 (total 7)	1.7 ± 0.8	1.5 ± 1.5	0.771	1.7 ± 0.9	2.9 ± 1.2	<0.001
SCORTEN Day 1 (% of ≥2)	32 (22.2%)	4 (30.8%)	0.497	36 (22.9%)	5 (45.5%)	0.139
SCORTEN Day 7 (% of ≥2)	86 (59.7%)	5 (38.5%)	0.153	91 (58.0%)	9 (81.8%)	0.202

Table 3. (Continued) Prognosis factors of full recovery, sequelae, and mortality. *SCAR, severe cutaneous adverse reaction; BMI, body mass index; OPD, out-patient department; ER, emergency room; 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; DHS, drug hypersensitivity syndrome; BSA, body surface area; WBC, white blood cells; Cr, creatinine; ALT, alkaline phosphatase; IVIG, intravenous immunoglobulin; ICU, intensive care unit; SCORTEN, SCORe of Toxic Epidermal Necrosis*

higher proportion of patients with poor prognosis (with sequelae or death). The factors associated with poor prognosis were SJS-TEN overlap, TEN as the SCAR phenotype. and carbapenems as the causative drugs.

To the best of our knowledge, this is the first large-scale study that has been conducted on beta-lactam antibiotic-induced SCAR. In 2014, a retrospective study on SCAR related to systemic antibiotics in 74 cases was published.[12] In this study, penicillins and cephalosporins were the most common causative agents of SJS, TEN, and acute generalized exanthematous pustulosis, and glycopeptides were the most common causative agents of DRESS. Although the ranking of penicillins and cephalosporins was reversed compared to that in our study, the most common causative antibiotic class, beta-lactam antibiotics, was identical. In that study, the mortality rate was the highest in the SJS and TEN groups, and it was associated with old age and underlying sepsis. The average latent period was 6.52 ± 4.59, 5 ± 3.52, and 11.3 ± 8.20 days for SJS, TEN, and DRESS, respectively, while it was 17.8 ± 25.8, 18.8 ± 28.2, and 24.7 ± 23.8, respectively, in our study. The latent period was longer in our study, but the longest latent period was observed in the DRESS subtype in both studies. The proportion of corticosteroid use was similar at 70.3% and 80.6%, respectively, but IVIG was used more frequently in our study (1.3% and 18.4%, respectively). The overall mortality was 20%, which was higher than 7.4% in our study, and mortality by SCAR type was TEN (66.7%), SJS or SJS-TEN overlap (20%), and DRESS (12%), which was also lower in our study (26.3% for TEN, 3.3% for SJS, 0% for SJS-TEN overlap, and 5.1% for DRESS. The average SCORTEN score was 1.25 in survivors and 2.77 in the dead; similarly, the SCORTEN score on day 7 was 1.7 and 2.9, respectively.[12]

The SCAR study was published in 2019, but it was also a retrospective review of electronic medical records of only 35 cases.[13] SCARs caused by all drugs were targeted, and antibiotics were the most common agents (88.1%). Among them, cephalosporins (23.7%) and penicillin (16.9%) were the most common culprit drugs, as shown in our study. In that study, the latent period was 6.2 days for SJS/TEN and 14.0 days for DRESS,

Variable	Univariate analysis OR (95% C·I.)	*P*-value	Multivariate analysis[a] OR (95% C·I.)	*P*-value
Age				
<60 years	1			
≥60 years	0.78 (0.32–1.91)	0.592		
Sex				
Female	1			
Male	1.12 (0.47–2.69)	0.800		
SCAR type				
SJS	1		1	
Overlap	2.62 (0.44–15.58)	0.290	35.61 (1.92–660.25)	**0.016**
TEN	10.19 (2.97–34.96)	**<0.001**	28.07 (2.56–307.19)	**0.006**
DRESS	0.75 (0.23–2.46)	0.639	2.13 (0.21–22.24)	0.527
Mucosal involvement				
No	1			
Yes	1.94 (0.65–5.79)	0.234		
Fever				
No	1			
Yes	1.89 (0.70–5.10)	0.209		
Highest serum Cr (mg/mL)	1.30 (1.01–1.67)	**0.046**	1.00 (0.64–1.56)	0.992
Highest serum ALT (IU/L)	1.00 (0.99–1.00)	0.978		
Administration of culprit (day)	0.93 (0.88–1.01)	0.106		
Previous exposure to culprit				
No	1			
Yes	3.00 (0.76–11.86)	0.117		
Time to symptom onset (day)	0.98 (0.94–1.01)	0.149		
Antibiotic class				
Penicillin	1		1	
Cephalosporin	0.66 (0.26–1.64)	0.368	0.94 (0.19–4.65)	0.938
Carbapenem	7.95 (1.17–53.82)	**0.034**	30.46 (1.47–632.84)	**0.027**
SCORTEN Day 1 (total 7)	1.52 (0.92–2.52)	0.106		
SCORTEN Day 7 (total 7)	1.71 (1.09–2.69)	**0.020**	2.05 (0.81–5.15)	0.129
SCORTEN Day 1 (% of ≥ 2)	2.10 (0.84–5.24)	0.112		
SCORTEN Day 7 (% of ≥ 2)	0.94 (0.39–2.27)	0.898		
Hospitalization (day)	1.01 (0.99–1.02)	0.169		
Comorbidities				
Other allergic disease	1.50 (0.39–5.82)	0.558		
Other drug hypersensitivity	1.03 (0.41–2.61)	0.946		
Chronic kidney disease	3.08 (0.70–13.44)	0.134		
Diabetes mellitus	1.29 (0.44–3.87)	0.638		
Hypertension	1.18 (0.46–3.04)	0.726		
Cancer	1.67 (0.49–5.64)	0.411		

Table 4. Factors associated with poor prognosis (sequelae or death) of beta-lactam-induced SCARs using binary logistic regression (univariate and multivariable analysis). *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; Cr, creatinine; ALT, alkaline phosphatase; SCORTEN, SCORe of Toxic Epidermal Necrosis.* [a]*Adjusted for age, sex, SCAR type, highest serum creatinine level, antibiotics class, and SCORTEN Day 7*

which were shorter than those in our study. Systemic corticosteroids were used in 71.4% of the patients, and IVIG was not administered. There was female preponderance in SJS and TEN, and male preponderance in DRESS, while there were no sex differences in our study.[13]

In another retrospective observational comparative study between antibiotic- and non-antibiotic-associated delayed cutaneous adverse drug reactions, 48% of the 84 patients were antibiotic-associated cases.[14] When compared with antibiotic-related SCAR in our study, age and sex were similar, while the latency period was longer in our study (11.0 vs. 6.0 days). As in our study, beta-lactam antibiotics (61.8% vs. 45.0%), especially cephalosporins, were the most common implicated drug. Mortality were lower in our study (7.4% vs. 10–20%).

Although studies on risk factors for drug allergy are still lacking, previous studies have suggested that female sex, age, systemic lupus erythematosus, and human immunodeficiency virus infection are risk factors.[15] Conversely, atopy is not considered a major risk factor for most drug allergies.[15] Risk factors for the development of SCAR or the poor prognosis of SCAR have been rarely studied, and risk factors for the occurrence of beta-lactam antibiotic-induced SCAR could not be analyzed in our study. However, analysis of risk factors related to poor prognosis showed that there was no statistical significance with sex, age, comorbidities, or other allergic diseases; only TEN subtype and carbapenem use were significant risk factors in our study.

Although antibiotics and anticonvulsants are known to be the most common causative drugs of SCAR,[15] few studies have been conducted on antibiotic-induced SCAR. The clinical features of antibiotic-induced SCAR have not been studied; thus, we have no clinical information regarding this. Moreover, although cotrimoxazole, allopurinol, carbamazepine, phenytoin, phenobarbital, and oxicam-NSAIDs are known as "high risk" for the development of SCAR,[16] the commonly listed culprit drugs are penicillins and cephalosporins in antibiotic-induced SCAR, not cotrimoxazole.[12,13] For the first time, carbapenem-induced SCAR was found to be associated with poor prognosis in our study. However, carbapenem is expected to be used in clinically severe and antibiotic-resistant patients. Therefore, it is likely that the prognosis was poor because patients who used carbapenems had severe baseline medical conditions, rather than because of a difference in the type of antibiotics. Although we considered the effect of comorbidities as a contributing factor in the univariate analysis, detailed patient conditions were not evaluated. Moreover, the number of patients with carbapenem-induced SCAR was small and larger-scale studies are required to confirm our result.

There are some limitations to our study. First, we only collected clinical data, and we did not study possible mechanisms. Therefore, this aspect needs to be further investigated. Secondly, the causative drugs were not certain. Since not all cases were confirmed by drug skin test or *in vitro* test, the culprit drug had to be presumed. In particular, it was more difficult to select a suspected drug when multiple drugs were administered simultaneously. In these cases, all suspected drugs used simultaneously were assumed to be causative agents based on expert judgment. Thirdly, we did not assess the effects of type or severity of infection for the prognosis of SCAR as unified and valid evaluation of infection severity is complicating. The association between specific beta-lactam antibiotics and outcome of SCAR needs to be clarified controlling these factors in the further study. Fourth, SCAR may be related to viral infection, but testing for this has not been performed. In the case of SJS/TEN, they may be related or mimic to herpes simplex virus (HSV) or Mycoplasma pneumonia infection. In addition, reactivation of human herpesvirus (HHV) is often seen in DRESS patients. Since the relationship between viral infection and SCAR cannot be ruled out, further investigation is needed in the next study.[17] Finally, the retrospective study design had limitations in predicting causal relationships.

In conclusion, we analyzed the clinical characteristics, common causative drugs, and risk factors of poor prognosis of beta-lactam antibiotic-induced SCARs, using large scale, nationwide data. SJS/TEN is the most common type of beta-lactam antibiotic-induced SCAR. Among the beta-lactam antibiotic-induced SCAR, prognosis was the most favorable in patients with DRESS and the worst in patients with TEN. The risk factors for

poor prognosis leading to sequelae or death were SJS-TEN overlap and TEN, and carbapenems as the causative agents.

SCAR is a serious and lethal disease, and beta-lactam antibiotic-related SCAR accounts for a large proportion of SCAR cases. In particular, SJS/TEN which is very severe SCARs with poor prognosis were common type in beta-lactam antibiotic-related SCARs. Therefore, more attention should be paid to monitoring skin reactions while using beta-lactam antibiotics. In addition, it was observed in this study that the prognosis may be worse when SCAR caused by carbapenem occurs. Careful observation is also necessary in patients taking carbapenem, and early discontinuation and treatment would be needed when symptoms develop. Moreover, in-depth research is required to understand the mechanism in order to prevent SCAR from happening in the future.

Abbreviations

BMI, body mass index; BSA, body surface area; DIHS, drug-induced hypersensitivity syndrome; DRESS, drug reaction with eosinophilia and systemic symptoms; IVIG, intravenous immune globulin; OR, odds ratio; SCAR, severe cutaneous adverse reactions; SJS, Stevens-Johnson syndrome; TEN, toxic epidermal necrolysis; WBC, white blood cell.

Funding

There is no funding source of this study.

Availability of data and materials

The data used in this paper is not public data and therefore cannot be disclosed.

Ethics approval

IRB approval number of the representative institution, Seoul National University Bundang Hospital is B-1802-450-401.

Authors' consent for publication

All authors consented to the publication of this paper.

Declaration of competing interest

Authors have no conflicts to disclose.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.waojou.2022.100738.

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