Disseminated intravascular coagulation in Stevens-Johnson syndrome and toxic epidermal necrolysis

Chun-Bing Chen, MD,[a,b,c,d,e,f,g] Tsun-Hao Hsu, MD,[a,b] Rosaline Chung-Yee Hui, MD, PhD,[a,b] Chun-Wei Lu, MD,[a,b,c,d,f] Wei-Ti Chen, MD,[a,b] Pin-Hsuan Chiang, MD,[a,b] Chuang-Wei Wang, PhD,[a,b,c,d,e] Shiow-Shuh Chuang, MD, PhD,[h] Jui-Yung Yang, MD,[h] Shih-Yi Yang, MD,[h] Shu-Ying Chang, MD,[h] Yen-Chang Hsiao, MD,[h] Kuo-Chin Kao, MD,[i,j] Han-Chung Hu, MD,[i,j] Ting-Shu Wu, MD, PhD,[k] Chao-Wei Hsu, MD, PhD,[l] David Hui-Kang Ma, MD, PhD,[m] Shin-Yi Chen, MD,[n] Ya-Chung Tian, MD,[o] Chi-Yuan Cheng, MS,[p] Chi-Hua Chen, MS, PhD,[p] Min-Hui Chi, MD,[a,b] Ming-Ying Wu, MD,[a,b] Ren-Feng Liu, MD,[a,b] Chi-Hui Wang, MD,[a,b] Ya-Ching Chang, MD,[a,b] Jing-Yi Lin, MD,[a,b] Hsin-Chun Ho, MD,[a,b] Yang Yu-Wei Lin,[a] Chee Jen Chang, PhD,[b,q,r] Yu-Jr Lin, BA,[b,q,r] Cheng-Lung Ku, PhD,[s,t] Shuen-Iu Hung, PhD,[b,e] and Wen-Hung Chung, MD, PhD,[a,b,d,e,f,g,u,v] for the Taiwan Severe Cutaneous Adverse Reaction Consortium

Taipei, Linkou, and Keelung, Taiwan

Background: Patients with Stevens-Johnson syndrome (SJS)/toxic epidermal necrolysis (TEN) have high mortality rates. Disseminated intravascular coagulation has been reported in SJS/TEN patients. The influence of this lethal complication in patients with SJS/TEN is not well known.

Objective: This study aimed to investigate the risk and outcomes of disseminated intravascular coagulation in patients with SJS/TEN.

Methods: We analyzed the disseminated intravascular coagulation profiles of patients receiving a diagnosis of SJS/TEN between 2010 and 2019.

From the Department of Dermatology, Drug Hypersensitivity Clinical and Research Center, Chang Gung Memorial Hospital, Linkou, Taipei, Keelung, Taoyuan[a]; College of Medicine,[b] Clinical Informatics Department of Respiratory Therapy, College of Medicine,[j] Research Services Center for Health Information,[q] and Clinical Informatics and Medical Statistics Research Center,[r] Chang Gung University, Taoyuan; Graduate Institute of Clinical Medical Sciences, College of Medicine, Chang Gung University, Kwei-Shan, Taoyuan[c]; Chang Gung Immunology Consortium,[d] Cancer Vaccine and Immune Cell Therapy Core Laboratory,[e] and Department of Ophthalmology,[m] Chang Gung Memorial Hospital, Linkou, Taoyuan; Immune-Oncology Center of Excellence,[f] Department of Nephrology, Kidney Research Center,[o] and Department of Pharmacy,[p] Chang Gung Memorial Hospital, Linkou; Department of Dermatology, Xiamen Chang Gung Hospital[g]; Department of Plastic and Reconstructive Surgery, The Burn Center,[h] Department of Thoracic Medicine,[i] and Department of Hepatogastroenterology, Liver Research Center,[l] Chang Gung Memorial Hospital, Taoyuan; and Department of Ophthalmology, Chang Gung Memorial Hospital, Keelung[n]; Division of Infectious Diseases, Department of Internal Medicine, Chang Gung Memorial Hospital, Chang Gung University College of Medicine, Kweishan, Taoyuan[k]; Laboratory of Human Immunology and Infectious Disease, Graduate Institute of Clinical Medical Sciences, Chang Gung University,[s] Department of Nephrology, Chang Gung Memorial Hospital,[t] Taoyuan; Department of Dermatology, Beijing Tsinghua Chang Gung Hospital, School of Clinical Medicine, Tsinghua University, Beijing[u]; and Department of Dermatology, Ruijin Hospital, School of Medicine, Shanghai Jiaotong University, Shanghai, China.[v]

Funding sources: Supported by research grants from the Ministry of Science and Technology, Taiwan (MOST 108-2314-B-182A-006-MY3 to CB Chen; (MOST 103-2321-B-182-001, MOST 104-2314-B-182A-148-MY3, MOST 104-2325-B-182A-006, MOST 105-2325-B-182A-007, MOST 106-2314-B-182A-037-MY3, MOST 106-2622-B-182A-003-CC2, MOST 107-2622-B-182A-001-CC2, MOST 108-2314-B-182A-104-MY3, MOST 108-2320-B-182A-023-MY3, MOST 108-2320-B-182A-024-MY2, MOST 109-2320-B-182A-008 -MY3 to WH Chung) and Chang Gung Memorial Hospital, Taiwan (CMRPG2H0081, CMRPG2J0221, CMRPG2J0222, NMRPG2J6012, NMRPG2J6013, CIRPG2I0011, CIRPG2I0012, CIRPG2I0013 to CB Chen; CIRPD1D0032 to CJ Chang; CIRPG3I0022, CIRPG3I0023, CIRPG3I0042, CIRPG3I0043, CLRPG3E0036, CLRPG3J0012, CMRPG3I0382, CORPG3J0322, CLRPG2E0053, CMRPG3D0363, CORPG3F0042~3, NCRPG3G0023, NCRPG3GS023, NMRPG3G6293, NMRPG3J6062, NMRPG3J6063, NMRPG3K0521, OMRPG3E0041 to WH Chung).

Conflicts of interest: None disclosed.

IRB approval status: Reviewed and approved by the IRB and the ethics committee of Chang Gung Memorial Hospital, in compliance with Taiwanese law.

Accepted for publication August 14, 2020.

Correspondence to: Wen-Hung Chung, MD, PhD, Department of Dermatology, Drug Hypersensitivity Clinical and Research Center, Chang Gung Memorial Hospital, No. 5, Fusing St, Taoyuan 333, Taiwan. E-mail: wenhungchung@yahoo.com or chung1@cgmh.org.tw.

Published online August 20, 2020.

0190-9622/$36.00

© 2020 by the American Academy of Dermatology, Inc.

https://doi.org/10.1016/j.jaad.2020.08.065

Results: We analyzed 150 patients with SJS/TEN (75 with SJS, 22 with overlapping SJS/TEN, and 53 with TEN) and their complete disseminated intravascular coagulation profiles. Disseminated intravascular coagulation was diagnosed in 32 patients (21.3%), primarily those with TEN. It was significantly associated with systemic complications, including gastrointestinal bleeding, respiratory failure, renal failure, liver failure, infection, and bacteremia. Additionally, SJS/TEN patients with disseminated intravascular coagulation had elevated procalcitonin levels. Among patients with SJS/TEN, disseminated intravascular coagulation was associated with a greater than 10-fold increase in mortality (78.1% vs 7%).

Limitations: The study limitations include small sample size and a single hospital system.

Conclusion: Disseminated intravascular coagulation is a potential complication of SJS/TEN and associated with higher mortality. Early recognition and appropriate management of this critical complication are important for patients with SJS/TEN. (J Am Acad Dermatol 2021;84:1782-91.)

Key words: coagulopathy; disseminated intravascular coagulation; severe cutaneous adverse reactions; Stevens-Johnson syndrome; thrombocytopenia; toxic epidermal necrolysis.

INTRODUCTION

Stevens-Johnson syndrome (SJS)/toxic epidermal necrolysis (TEN) is a potentially fatal, drug-induced mucocutaneous disease. Skin detachment greater than 30% is defined as TEN, 10% to 30% is an overlap of SJS and TEN, and less than 10% is SJS.[1] The skin lesions are initially characterized as a generalized, painful, dusky red, erythematous rash with atypical target lesions that progressively coalesce. Evolution of flaccid blisters, which can be easily detached by pressure or friction, leads to a large area of exposed erythematous oozing dermis.[2] Histopathology typically shows widespread keratinocyte apoptosis, full-thickness epidermal necrosis, and detachment with a sparse dermal monocytic (predominantly T-cell) infiltrate.[3] This condition is associated with high mortality (10%-50%) and usually results in lifelong sequelae.[4]

Disseminated intravascular coagulation is a syndrome characterized by the systemic activation of blood coagulation, which generates intravascular fibrin, leading to thrombosis of small- and medium-sized vessels and, eventually, organ dysfunction.[5] It may occur as a complication of systemic inflammation. The main clinical manifestations related to disseminated intravascular coagulation include bleeding (64.4%), renal dysfunction (24.6%), liver dysfunction (18.6%), respiratory dysfunction (16.1%), shock (14.4%), thromboembolic phenomena (6.8%), and central nervous system involvement (1.7%).[6] The cutaneous manifestations of disseminated intravascular coagulation include petechiae, purpura, palpable variants of both, acral cyanosis, hemorrhagic bullae, purpura fulminans, subcutaneous dissecting hematomata, or bleeding from the wound and were the presenting sign in half of the cases.[7]

CAPSULE SUMMARY

- Disseminated intravascular coagulation is a potential complication after Stevens-Johnson syndrome/toxic epidermal necrolysis.
- Patients with Stevens-Johnson syndrome/toxic epidermal necrolysis complicated by disseminated intravascular coagulation had a significantly higher risk of multiple organ failure and mortality. Therefore, early recognition and appropriate management of disseminated intravascular coagulation are important for patients with Stevens-Johnson syndrome/toxic epidermal necrolysis.

Several reports have shown disseminated intravascular coagulation as a severe complication in patients with SJS/TEN. Most TEN patients with disseminated intravascular coagulation have a poor prognosis.[8,9] Kvasnicka et al[8] observed disseminated intravascular coagulation signs in relation to the severity of the clinical conditions in 8 TEN patients. The alternation of hemostasis and interrelated biological systems, such as activation of components of complement, kinins, and immunoglobins, may affect the outcome of patients with TEN.[8] However, disseminated intravascular coagulation in SJS/TEN patients has rarely been examined, and the influence of this potentially lethal complication in SJS/TEN is not well known. In this study, we aimed to investigate the risk and outcome of SJS/TEN patients with disseminated intravascular coagulation.

Abbreviations used:

CI: confidence interval
OR: odds ratio
SJS: Stevens-Johnson syndrome
TEN: toxic epidermal necrolysis

METHODS

SJS/TEN patients were enrolled from 2010 to 2019 at Chang Gung Memorial Hospital, which is the largest medical health system in Taiwan and receives SJS/TEN referral cases from other hospitals. Patients were eligible initially if they received a diagnosis of SJS/TEN according to the phenotypic criteria of the Registry of Severe Cutaneous Adverse Reaction study.[10-12] Only participants with probable or definite cases of SJS/TEN were enrolled. The diagnostic evaluation was further supported by laboratory assessments of skin biopsies with direct and indirect immunofluorescence using anti-intercellular substances and anti—basement membrane zone autoantibodies, as well as detection of blister granulysin levels to exclude other autoimmune bullous diseases.[13]

Disseminated intravascular coagulation profiles (including platelet count, prothrombin time, activated partial thromboplastin time, D-dimer, fibrinogen, and fibrin degradation products) of enrolled patients were evaluated on admission and twice a week during hospitalization. Disseminated intravascular coagulation was diagnosed according to the Japanese Association for Acute Medicine criteria.[14,15] Demographic data included underlying diseases, TEN-specific severity-of-illness score (Score of Toxic Epidermal Necrosis) on admission, and bacterial and fungal cultures from the bloodstream, skin wounds, or other infected sites. Complications and prognosis were evaluated.[16]

Statistical analysis

Statistical analyses were performed with R, version 3.6.2 (The R Foundation for Statistical Computing, Vienna, Austria). Logistic regression analysis was used to compare differences between SJS/TEN patients with or without disseminated intravascular coagulation and differences in management between surviving or dead patients with disseminated intravascular coagulation. Odds ratios (ORs) and 95% confidence intervals (CIs) were also calculated. The Kaplan-Meier method with log-rank test was performed to analyze the hazard ratio and 95% CI of the overall survival between patients with or without disseminated intravascular coagulation. Two-sided $P < .05$ was considered significant in all statistical analyses.

RESULTS

Patient characteristics

We enrolled a total of 150 patients with SJS/TEN (75 with SJS [50.0%], 22 with SJS/TEN overlapping [14.7%], and 53 with TEN [35.3%]) with complete disseminated intravascular coagulation profiles after excluding patients with known clotting disorders (n = 3) or who were undergoing anticoagulant therapy (n = 2) (Supplemental Fig 1 and Supplemental Table I available via Mendeley at https://data.mendeley.com/datasets/gpcj4b3wtk/1). Among 150 SJS/TEN patients, 32 (21.3%) developed disseminated intravascular coagulation during the active stage of SJS/TEN (Table I). These patients were older (average 62.3 years), were predominantly women (62.5%), had high averages for the Score of Toxic Epidermal Necrosis (4.0), and had large total body surface area involvement (TEN [81.3%]). The average duration for patients to develop disseminated intravascular coagulation was 4.7 days (standard deviation 3.9 days) after admission and 7.8 days (standard deviation 4.4 days) from the index date. Twelve SJS/TEN patients (8.0%) developed disseminated intravascular coagulation on admission. These 32 SJS/TEN patients with disseminated intravascular coagulation showed a high score for the disorder (average 5.3; standard deviation 1.3). The disseminated intravascular coagulation profiles showed decreased platelet count (90.6%), increased fibrin degradation products (56.3%), elevated prothrombin time ratio (65.6%), elevated D-dimer level (62.5%), and decreased fibrinogen level (12.5%). A higher percentage of patients demonstrated high systemic inflammatory response syndrome scores (84.4%), including tachycardia (68.8%), tachypnea (68.8%), fever or hypothermia (50.0%), and leukocytosis, leukopenia, or bandemia (18.8%). Laboratory data showed a high rate of acute kidney injury (59.4%), hepatic impairment (28.1%), and procalcitonin levels (78.1%). SJS/TEN patients with disseminated intravascular coagulation were prone to easy bleeding and poor wound healing (Supplemental Fig 2). Patients with disseminated intravascular coagulation had a mortality rate of 78.1% (Table I).

Complications and mortality associated with disseminated intravascular coagulation in SJS/TEN patients

Complications observed in SJS/TEN patients with disseminated intravascular coagulation included gastrointestinal bleeding (78.2%), respiratory failure (71.9%), renal failure (34.4%), liver failure (25.0%),

Table I. Demographic variables of Stevens-Johnson syndrome/toxic epidermal necrolysis patients with disseminated intravascular coagulation (n = 32)

Characteristic	SJS/TEN patients with DIC (n = 32)
Age, mean ± SD, y	62.3 ± 22.2
Sex (men)	12 (37.5)
Time between disease onset to admission, mean ± SD, d	3.0 ± 1.6
Underlying diseases	
Diabetes	8 (25.0)
Hypertension	12 (37.5)
Cardiovascular disease	5 (15.6)
Chronic kidney disease	13 (40.6)
Chronic liver disease	3 (9.3)
Malignancy	6 (18.8)
Neurologic disease	5 (15.6)
Gout	5 (15.6)
SJS/TEN	1 (3.1)
Disease classification	
SJS	2 (6.3)
SJS/TEN overlapping	4 (12.5)
TEN	26 (81.3)
SCORTEN, mean ± SD	4.0 ± 1.4
SIRS*	27 (84.4)
Heart rate >90/min	22 (68.8)
Respiratory rate >20/min	22 (68.8)
Fever or hypothermia	16 (50.0)
WBC (>10,000 or <4000/mm^3) or bandemia (>10%)	6 (18.8)
DIC laboratory profile	
Platelet count ($\times 10^3/\mu$L)	
≥80, but <120 or >30% reduction*	4 (12.5)
<80, or >50% reduction†	25 (78.1)
FDP (μg/mL)	
>10 but <25*	7 (21.9)
≥25†	11 (34.4)
PT ratio ≥1.2*	21 (65.6)
D-dimer >500 ng/mL	20 (62.5)
Fibrinogen <190 mg/dL	4 (12.5)
JAAM DIC score, mean ± SD*,‡	5.3 ± 1.3
Onset of DIC from admission, mean ± SD, d	4.7 ± 3.9
Other laboratory data	
Acute kidney injury¶	19 (59.4)
Hepatic impairment§	9 (28.1)
Procalcitonin >2 ng/mL	25 (78.1)
Bacteremia	9 (28.1)
Mortality	25 (78.1)

Data are presented as No. (%) unless otherwise indicated.

DIC, disseminated intravascular coagulation; *FDP*, fibrin degradation products; *JAAM*, Japanese Association for Acute Medicine; *PT*, prothrombin time; *SCORTEN*, Score of Toxic Epidermal Necrosis; *SD*, standard deviation; *SIRS*, systemic inflammatory response syndrome; *SJS*, Stevens-Johnson syndrome; *TEN*, toxic epidermal necrolysis; *WBC*, white blood cell.

*Scored 1 point according to JAAM disseminated intravascular coagulation criteria, including systemic inflammatory response syndrome score greater than or equal to 3, platelet count greater than or equal to 80 $\times$ 10^3/μL to less than 120 $\times$ 10^3/μL or greater than 30% decrease within 24 hours, fibrin/fibrinogen degradation products greater than or equal to 10 μg/mL to less than 25 μg/mL, and prothrombin time (value of patient/normal value) greater than or equal to 1.2 seconds.

†Scored 3 points according to JAAM disseminated intravascular coagulation criteria, including platelet count less than 80 $\times$ 10^3/μL or greater than 50% decrease within 24 hours and fibrin/fibrinogen degradation products greater than or equal to 25 mg/L.

‡Disseminated intravascular coagulation was diagnosed according to the JAAM disseminated intravascular coagulation diagnostic criteria using platelet count, fibrin/fibrinogen degradation products, prothrombin time, and systemic inflammatory response syndrome score. A total score greater than or equal to 4 meets the diagnosis of disseminated intravascular coagulation.

¶The value of creatinine was 1.5 times greater than the normal value range (0.4-1.5 mg/dL) after drug intake.

§Values were 2 times greater than normal for glutamic-oxaloacetic transaminase, glutamic-pyruvic transaminase, and total bilirubin.

Table II. Complications and mortality in patients with Stevens-Johnson syndrome/toxic epidermal necrolysis (n = 150)

Characteristic	Total (n = 150)	DIC (n = 32)	Non-DIC (n = 118)	*P* value	Odds ratio (95% CI)
Complication					
Gastrointestinal bleeding	49 (32.7)	25 (78.2)	24 (20.3)	<.001	13.99 (5.41-36.19)
Rhabdomyolysis	1 (0.7)	1 (3.3)	0	>.99	—
Respiratory failure	31 (20.7)	23 (71.9)	8 (6.8)	<.001	35.14 (12.26-100.72)
Acute respiratory distress syndrome	2 (1.3)	1 (3.3)	1 (0.8)	.35	3.77 (0.23-62.06)
Renal failure	16 (10.7)	11 (34.4)	5 (4.2)	<.001	11.84 (3.73-37.58)
Liver failure	10 (6.7)	8 (25.0)	2 (1.7)	<.001	19.33 (3.86-96.78)
Infection*	57 (38.7)	28 (87.5)	29 (24.6)	<.001	21.48 (6.95-66.39)
Bacteremia	15 (10.0)	9 (28.1)	6 (5.1)	.001	7.30 (2.37-22.53)
Indicator for sepsis					
Procalcitonin >2 ng/mL	35 (23.3)	25 (78.1)	11 (9.3)	<.001	34.74 (12.24-98.57)
Mortality	33 (22.0)	25 (78.1)	8 (6.8)	<.001	49.12 (16.29-148.03)

Data are presented as No. (%).
CI, Confidence interval; *DIC*, disseminated intravascular coagulation.
*Infection is defined as the presence of clinical symptoms/signs of infection with a positive culture result identified from blood, wounds, sputum, urine, pleural effusion, central venous catheter, stool, or ascites.

rhabdomyolysis (3.3%), acute respiratory distress syndrome (3.3%), infection (87.5%), and bacteremia (28.1%). Logistic regression analysis comparing SJS/TEN patients with and without disseminated intravascular coagulation showed significantly higher risk of systemic complications with gastrointestinal bleeding (OR 13.99; 95% CI 5.41-36.19; $P < .001$), respiratory failure (OR 35.14; 95% CI 12.26-100.72; $P < .001$), renal failure (OR 11.84; 95% CI 3.73-37.58; $P < .001$), liver failure (OR 19.33; 95% CI 3.86-96.78; $P < .001$), infection (OR 21.48; 95% CI 6.95-66.39; $P < .001$), and bacteremia (OR 7.30; 95% CI 2.37-22.53; $P = .001$). Laboratory examination showed a higher rate of elevated procalcitonin level (OR 34.74; 95% CI 12.24-98.57; $P < .001$). There was significantly higher mortality in patients with disseminated intravascular coagulation (OR 49.12; 95% CI 16.29-148.03; $P < .001$) (Table II). The survival probability of SJS/TEN patients with disseminated intravascular coagulation was significantly reduced the first few weeks after admission. The Kaplan-Meier curves for the probability of survival were evaluated (Fig 1). SJS/TEN patients with disseminated intravascular coagulation had a 16.80-fold higher risk of mortality during the first month after admission (hazard ratio 16.80; 95% CI 6.20-45.52; $P < .001$). Most patients who died had higher disseminated intravascular coagulation scores early (within 10 days), which persisted until death. In contrast, surviving patients usually had a gradual decrease in disseminated intravascular coagulation score. The sequential change of disseminated intravascular coagulation profiles in representative surviving or dead patients with SJS/TEN is demonstrated in Supplemental Fig 3.

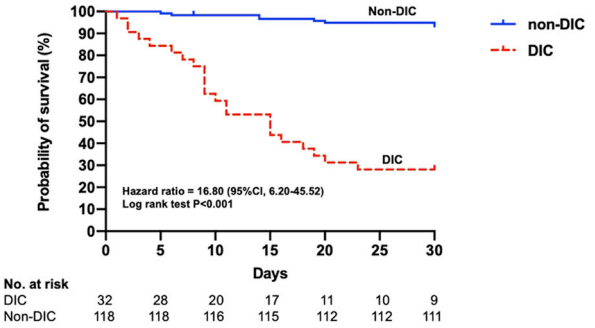

Fig 1. Kaplan-Meier curves for probability of survival in Stevens-Johnson syndrome/toxic epidermal necrolysis patients with disseminated intravascular coagulation. Overall survival was compared in patients with disseminated intravascular coagulation (n = 32) and without it (n = 118), using the Kaplan-Meier method. The curve showed that patients with disseminated intravascular coagulation had a significant higher risk for mortality during the first month of hospitalization (hazard ratio 16.80; 95% confidence interval 6.20-45.52; $P < .001$). *CI*, Confidence interval; *DIC*, disseminated intravascular coagulation.

Infectious pathogens identified among SJS/TEN patients with disseminated intravascular coagulation

There were 83 positive culture results during the hospitalization of the 32 SJS/TEN patients with disseminated intravascular coagulation. Twenty-eight patients (90.9%) had at least 1 documented infection with a positive culture result. Nine patients (28.1%) had a bloodstream infection (bacteremia), and 6 had polymicrobial bloodstream infections. The most common microorganisms identified from blood cultures were *Staphylococcus*

Table III. Management of Stevens-Johnson syndrome/toxic epidermal necrolysis patients with disseminated intravascular coagulation (n = 32)

Management	Total (n = 32)	Surviving (n = 7)	Dead (n = 25)	*P* value
Blood transfusion				
Cryoprecipitate	1 (3.1)	0	1 (4.0)	>.99
Fresh frozen plasma	23 (71.9)	4 (57.1)	20 (80.0)	.22
Platelet	15 (46.9)	2 (28.6)	14 (56.0)	.21
Packed RBCs	22 (68.8)	5 (15.6)	19 (76.0)	.81
Antibiotics				
Cephalosporin	16 (50.0)	4 (57.1)	12 (48.0)	.67
Penicillin	13 (40.6)	3 (42.9)	10 (40.0)	.89
Carbapenem	16 (50.0)	4 (57.1)	12 (48.0)	.67
Aminoglycosides	7 (21.9)	0	7 (28.0)	>.99
Quinolone	7 (21.9)	1 (14.3)	6 (24.0)	.59
Glycopeptides	25 (78.1)	5 (71.4)	20 (80.0)	.63
Tetracycline	3 (9.4)	0	3 (12.0)	>.99
Linezolid	2 (6.3)	0	2 (8.0)	>.99
Daptomycin	1 (3.1)	0	1 (4.0)	>.99
Colistin	2 (6.3)	1 (14.3)	1 (4.0)	.35
Clindamycin	2 (6.3)	1 (14.3)	1 (4.0)	.35
Metronidazole	5 (15.6)	1 (14.3)	4 (16.0)	.91
Antifungal agents	14 (43.8)	2 (28.6)	12 (48.0)	.37
Immunomodulant				
Corticosteroid	16 (50.0)	4 (57.1)	12 (48.0)	.67
Anti-TNF-α inhibitors	4 (12.5)	1 (14.3)	3 (12.0)	.87
Intravenous immunoglobulin	5 (15.5)	0	5 (20.0)	>.99
Supportive care without immunomodulant	7 (21.9)	2 (28.6)	5 (20.0)	.63

Data are presented as No. (%).
RBC, Red blood cell; *TNF*, tumor necrosis factor.

aureus (25.0%; n = 4), *Klebsiella pneumoniae* (25.0%; n = 4), and *Acinetobacter baumannii* (25.0%; n = 4). There were 33 positive culture results from skin wounds. *Enterobacter cloacae* (18.2%; n = 6), *S aureus* (15.2%; n = 5), and *A baumannii* (11.2%; n = 4) were the most common microorganisms identified from skin wounds. Details about the microorganisms in SJS/TEN patients with disseminated intravascular coagulation are shown in Supplemental Table II. Resistant strains, including 8 vancomycin-resistant *Enterococci,* 8 multidrug-resistant *A baumannii*, and 7 methicillin-resistant *S aureus*, were observed.

Management of SJS/TEN patients with disseminated intravascular coagulation

All patients discontinued the causative agents after admission. There were no differences between the use of immunomodulants (corticosteroid, anti–tumor necrosis factor α inhibitors, or intravenous immunoglobulin) or supportive care alone in survival rates among SJS/TEN patients with disseminated intravascular coagulation (Table III). All the SJS/TEN patients with disseminated intravascular coagulation received at least 1 systemic antibiotic treatment based on antibiotic susceptibility testing of the culture. Blood component therapy with cryoprecipitate (3.1%; n = 1), fresh frozen plasma (71.9%; n = 23), platelets (46.9%; n = 15), and packed red blood cells (68.8%; n = 22) were transfused in 27 patients with disseminated intravascular coagulation (84.4%) to treat coagulopathy and bleeding. No patient with disseminated intravascular coagulation received anticoagulant agents. There were no statistical differences in antibiotic use and blood component treatment between the surviving and dead patients with disseminated intravascular coagulation.

DISCUSSION

In this study, we evaluated the risk and influence of disseminated intravascular coagulation in 150 SJS/TEN patients during a decade. We found that disseminated intravascular coagulation, a potentially lethal complication, was not rare in SJS/TEN (especially TEN) patients. SJS/TEN patients with disseminated intravascular coagulation frequently had associated bacteremia and elevated procalcitonin levels, significantly complicated by subsequent

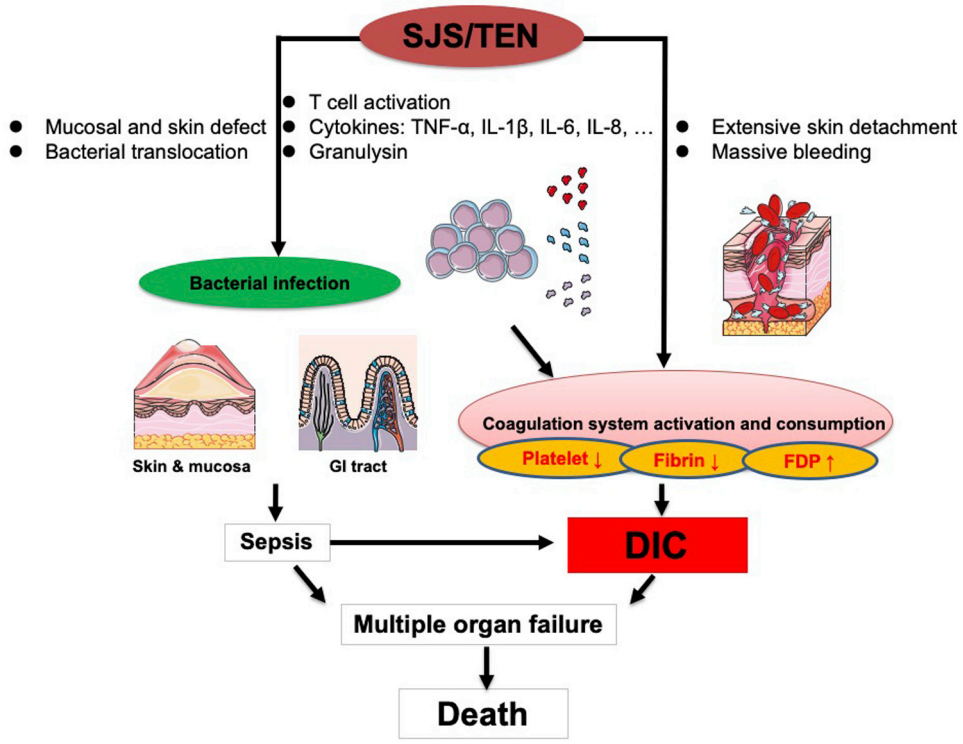

Fig 2. Proposed pathomechanisms of disseminated intravascular coagulation in Stevens-Johnson syndrome/toxic epidermal necrolysis. Stevens-Johnson syndrome/toxic epidermal necrolysis is considered an immunomediated reaction with T-cell activation, cytokine storms, and granulysin toxicity. The release of massive amounts of proinflammatory cytokines into systemic circulation predisposes to a procoagulant status. Severe sepsis is a well-known cause of disseminated intravascular coagulation. Infection is also one of the most common causes of mortality in patients with Stevens-Johnson syndrome/toxic epidermal necrolysis. Patients with the disease and extensive mucosal and skin detachment were much more susceptible to bacterial translocation, infection, and sepsis. Additionally, such patients have extensive skin detachment and massive tissue damage, similar to that of burn patients. These patients could have poor wound healing and bleeding, causing coagulation system activation and consumption. These reactions together could further cause coagulation system activation and consumption, resulting in disseminated intravascular coagulation, and further progress to multiple organ dysfunction and death. *DIC*, Disseminated intravascular coagulation; *FDP*, fibrin degradation products; *GI*, gastrointestinal; *IL*, interleukin; *SJS*, Stevens-Johnson syndrome; *TEN*, toxic epidermal necrolysis; *TNF*, tumor necrosis factor.

gastrointestinal bleeding events and multiple organ failures and associated with high mortality.

Disseminated intravascular coagulation is characterized by systemic activation of coagulation, insufficiently controlled by natural anticoagulation mechanisms, leading to the intravascular deposition of fibrin in the vasculature and the simultaneous consumption of coagulation factors and platelets.[17] Hematologic disturbance, including thrombocytopenia, leucopenia, and anemia, has been reported in TEN cases.[18] The underlying causes of disseminated intravascular coagulation include severe infection, hematologic malignancy, solid-tumor cancer, massive tissue damage, burns, and rhabdomyolysis. Furthermore, there are reports of severe TEN cases with disseminated intravascular coagulation. In a study of 21 TEN cases, Rajaratnam et al[19] reported 100% mortality in the 4 cases with disseminated intravascular coagulation. Other studies have also reported the manifestation of disseminated intravascular coagulation in SJS/TEN patients.[9,20] Disseminated intravascular coagulation was reported in a drug reaction with eosinophilia and systemic symptoms.[21] Therefore, it could manifest as a fatal complication in cases with severe adverse drug reactions, especially in TEN cases. For patients partially fulfilling the Japanese Association for Acute Medicine disseminated intravascular coagulation criteria, there was still a risk of progressing into overt disseminated intravascular coagulation at a later

stage. The Score of Toxic Epidermal Necrosis, a well-known predictor of mortality for SJS/TEN, was also evaluated in this study.[16,22] The mortality in SJS/TEN patients with disseminated intravascular coagulation in this study was higher (78.1%) than that estimated by the Score of Toxic Epidermal Necrosis (58.3%) (average score 4.0).[16] The Japanese Association for Acute Medicine scoring system has higher sensitivity for a disseminated intravascular coagulation diagnosis than other diagnostic criteria.[23,24] Because SJS/TEN is a potentially life-threatening disease, the diagnostic test with higher sensitivity may be used to recognize individuals with high risk.

Here, we propose several possible pathomechanisms for disseminated intravascular coagulation in patients with SJS/TEN, including severe infection, massive tissue damage (extensive skin detachment), and severe inflammation (cytokine storms) (Fig 2). First, severe sepsis is a well-known risk for disseminated intravascular coagulation.[25] Infection is also one of the most common causes of mortality in SJS/TEN patients.[1] SJS/TEN patients with extensive mucosal and skin detachment are much more susceptible to infection (from the skin or gastrointestinal tract) and sepsis.[26,27] Second, cytokine storms, which have been demonstrated in systemic infections, severe burns, trauma, and allergies, can be associated with disseminated intravascular coagulation.[28-31] SJS/TEN is considered an immunomediated reaction with T-cell activation, cytokine storms, and granulysin toxicity. Inflammation of internal mucosal surfaces, such as the gastrointestinal and respiratory tracts, commonly occurs in SJS/TEN patients. Internal involvement may be caused by the release of massive amounts of proinflammatory cytokines into systemic circulation.[32] One report comparing plasma of SJS/TEN patients with that of individuals without the disease showed a marked increase in the thrombin-antithrombin complexes, prothrombin fragments F1.2, platelet microparticles, and protein C levels, with a corresponding decrease in plasminogen activator inhibitor 1 and antithrombin levels, which are suggestive of a procoagulant status.[33] Moreover, proinflammatory cytokines, including tumor necrosis factor α; interleukin 1β, 2, 6, and 8; and interferon (IFN)-γ, are reported to increase the inflammatory response and induce coagulation in disseminated intravascular coagulation.[29,34] SJS/TEN patients have large skin defects and massive tissue damage, similar to burn patients. These patients could have poor wound healing and bleeding, causing coagulation system activation and consumption.[30] T-cell activation and the release of cytokines predispose to the immunomediated activation of coagulation exacerbated by massive tissue damage or sepsis that results in disseminated intravascular coagulation.[33]

The cornerstone of therapy in disseminated intravascular coagulation is the treatment of underlying disease.[35] Identification and prompt withdrawal of the culprit drug remains the key management of SJS/TEN. Severe infection and sepsis remain some of the most common causes of mortality in SJS/TEN patients.[36] Bacteremia may affect 30% of SJS/TEN patients and is associated with increased mortality and intensive care unit admission, and longer hospitalizations.[37] Antibiotic use for sepsis control has been another critical issue for managing and preventing disseminated intravascular coagulation caused by severe infection.[38] Generally, prophylactic antibiotics are not advised because they are possible culprit drugs for SJS/TEN.[27,39,40] However, empirical antimicrobial therapy should be initiated early if sepsis is suspected.[37,41] Therefore, when the use of antibiotics is inevitable, the selection of structurally different alternatives from the culprit drug is important to avoid rechallenge and recurrence.[42] Procalcitonin is superior to C-reactive protein in detecting systemic bacterial infections and guiding antibiotic treatment in SJS/TEN patients.[37,43] However, the implication of procalcitonin findings should be cautiously interpreted because procalcitonin level could be elevated in SJS/TEN patients without infections or renal failure.[44,45] Appropriate broad-spectrum antibiotic use with a de-escalation strategy is suggested if there is high clinical suspicion of sepsis to cover multidrug-resistant pathogens, similar to the treatment for patients with severe burn.[45,46]

Blood component therapy could decrease the risk of bleeding in disseminated intravascular coagulation, but platelet and coagulation protein transfusions should be reserved for patients with bleeding and should not be ordered according to laboratory results alone.[35] In general, platelet transfusion is indicated to maintain a platelet count of greater than $50 \times 10^3/\mu L$; fresh frozen plasma is administered to maintain prothrombin and activated partial-thromboplastin times less than 1.5 times the normal control time; fibrinogen is administered to maintain a fibrinogen level of greater than 150 mg/dL.[38,47] Despite the risk of development of thromboembolism in disseminated intravascular coagulation, prophylactic anticoagulation is still controversial.[38] In contrast, anticoagulation with low-molecular-weight heparin may be considered in cases of disseminated intravascular coagulation in which thrombosis predominates.[35] Anticoagulation therapy is also recommended for immobilized TEN patients with a high risk of deep vein thrombosis and pulmonary emboli.[48]

Currently, there are no optimal treatment guidelines for SJS/TEN. In this study, we did not identify differences among treatment with immunomodulants or supportive care in SJS/TEN patients with disseminated intravascular coagulation. Appropriate immunomodulants to suppress the production of inflammatory cytokines could be effective in treating SJS/TEN.[49,50] Systemic corticosteroids are the most common treatment option, but the use of corticosteroids has not shown a definite survival benefit.[51-53] Cyclosporine has been found to reduce mortality.[54] Intravenous immunoglobulin is another commonly used treatment for SJS/TEN, especially for pediatric patients.[49] There have also been an increasing number of reports regarding the benefits of anti−tumor necrosis factor α biologic agents in the treatment of SJS/TEN patients.[55] In our previous randomized controlled trial, anti−tumor necrosis factor α agents (etanercept) improved clinical outcomes, including mortality, skin healing time, and gastrointestinal hemorrhage complications, in SJS/TEN patients.[56]

There are some limitations in this study. First, it was performed in a single health system with a limited sample size, despite that SJS/TEN is a relatively rare disease. Second, prophylactic anticoagulant therapy was not administered to SJS/TEN patients with disseminated intravascular coagulation. These limitations might have affected the generalizability of our results to other centers and populations. Nonetheless, there are some strengths of our study. To our knowledge, it is the first and largest study to evaluate the risk of disseminated intravascular coagulation in SJS/TEN patients. Patients were managed in the same center with the same protocol, which could avoid bias attributed to center effect.

In conclusion, disseminated intravascular coagulation is not rare after SJS/TEN. SJS/TEN patients with disseminated intravascular coagulation had significantly associated subsequent complications and mortality. Early recognition and appropriate intervention of this challenging complication are important in SJS/TEN treatment.

REFERENCES

1. Roujeau JC, Stern RS. Severe adverse cutaneous reactions to drugs. *N Engl J Med*. 1994;331(19):1272-1285.
2. Revuz J, Roujeau JC, Guillaume JC, Penso D, Touraine R. Treatment of toxic epidermal necrolysis. Creteil's experience. *Arch Dermatol*. 1987;123(9):1156-1158.
3. Paquet P, Piérard GE, Quatresooz P. Novel treatments for drug-induced toxic epidermal necrolysis (Lyell's syndrome). *Int Arch Allergy Immunol*. 2005;136(3):205-216.
4. Paulmann M, Mockenhaupt M. Severe drug hypersensitivity reactions: clinical pattern, diagnosis, etiology and therapeutic options. *Curr Pharm Des*. 2016;22(45):6852-6861.
5. Taylor FB Jr, Toh CH, Hoots WK, Wada H, Levi M, Scientific Subcommittee on Disseminated Intravascular Coagulation (DIC) of the International Society on Thrombosis and Haemostasis (ISTH). Towards definition, clinical and laboratory criteria, and a scoring system for disseminated intravascular coagulation. *Thromb Haemost*. 2001;86(5):1327-1330.
6. Siegal T, Seligsohn U, Aghai E, Modan M. Clinical and laboratory aspects of disseminated intravascular coagulation (DIC): a study of 118 cases. *Thromb Haemost*. 1978;39(1):122-134.
7. Robboy SJ, Mihm MC, Colman RW, Minna JD. The skin in disseminated intravascular coagulation. Prospective analysis of thirty-six cases. *Br J Dermatol*. 1973;88(3):221-229.
8. Kvasnicka J, Rezác J, Svejda J, et al. Disseminated intravascular coagulation associated with toxic epidermal necrolysis (Lyell's syndrome). *Br J Dermatol*. 1979;100(5):551-558.
9. Arellano Ocampo F, Pérez Martín MA, Rodríguez MT, Ramales E. [Toxic epidermal necrosis. Review of the theme and presentation of 20 cases]. *Med Cutan Ibero Lat Am*. 1979;7(1-3):31-43.
10. Roujeau JC. Clinical heterogeneity of drug hypersensitivity. *Toxicology*. 2005;209(2):123-129.
11. Auquier-Dunant A, Mockenhaupt M, Naldi L, et al. Correlations between clinical patterns and causes of erythema multiforme majus, Stevens-Johnson syndrome, and toxic epidermal necrolysis: results of an international prospective study. *Arch Dermatol*. 2002;138(8):1019-1024.
12. Naranjo CA, Busto U, Sellers EM, et al. A method for estimating the probability of adverse drug reactions. *Clin Pharmacol Ther*. 1981;30(2):239-245.
13. Arbache ST, Nogueira TG, Delgado L, Miyamoto D, Aoki V. Immunofluorescence testing in the diagnosis of autoimmune blistering diseases: overview of 10-year experience. *An Bras Dermatol*. 2014;89(6):885-889.
14. Gando S, Iba T, Eguchi Y, et al. A multicenter, prospective validation of disseminated intravascular coagulation diagnostic criteria for critically ill patients: comparing current criteria. *Crit Care Med*. 2006;34(3):625-631.
15. Gando S, Saitoh D, Ogura H, et al. Natural history of disseminated intravascular coagulation diagnosed based on the newly established diagnostic criteria for critically ill patients: results of a multicenter, prospective survey. *Crit Care Med*. 2008;36(1):145-150.
16. Bastuji-Garin S, Fouchard N, Bertocchi M, Roujeau JC, Revuz J, Wolkenstein P. SCORTEN: a severity-of-illness score for toxic epidermal necrolysis. *J Invest Dermatol*. 2000;115(2):149-153.
17. Toh CH, Dennis M. Disseminated intravascular coagulation: old disease, new hope. *BMJ*. 2003;327(7421):974-977.
18. Goens J, Song M, Fondu P, Blum D, Achten G. Haematological disturbances and immune mechanisms in toxic epidermal necrolysis. *Br J Dermatol*. 1986;114(2):255-259.
19. Rajaratnam R, Mann C, Balasubramaniam P, et al. Toxic epidermal necrolysis: retrospective analysis of 21 consecutive cases managed at a tertiary centre. *Clin Exp Dermatol*. 2010;35(8):853-862.
20. Huang RY, Liu HN, Wong CK. [Stevens-Johnson syndrome: a review of 42 cases]. *Zhonghua Yi Xue Za Zhi (Taipei)*. 1993;51(3):225-230.
21. Miyazaki H, Yanagitani S, Matsumoto T, et al. Hypercoagulopathy with piperacillin administration in osteomyelitis. *Intern Med*. 2000;39(5):424-427.
22. Ho Y-L, Chang Y-T, Chu Y-T, Wu S-C. Performance of the SCORTEN in Taiwanese patients with Stevens-Johnson syndrome and toxic epidermal necrolysis. *Dermatol Sin*. 2010;28(1):15-20.

23. Gando S. The utility of a diagnostic scoring system for disseminated intravascular coagulation. *Crit Care Clin*. 2012; 28(3):373-388. vi.
24. Takemitsu T, Wada H, Hatada T, et al. Prospective evaluation of three different diagnostic criteria for disseminated intravascular coagulation. *Thromb Haemost*. 2011;105(1):40-44.
25. Semeraro N, Ammollo CT, Semeraro F, Colucci M. Sepsis, thrombosis and organ dysfunction. *Thromb Res*. 2012;129(3): 290-295.
26. de Prost N, Ingen-Housz-Oro S, Duong Ta, et al. Bacteremia in Stevens-Johnson syndrome and toxic epidermal necrolysis: epidemiology, risk factors, and predictive value of skin cultures. *Medicine (Baltimore)*. 2010;89(1):28-36.
27. Duong TA, Valeyrie-Allanore L, Wolkenstein P, Chosidow O. Severe cutaneous adverse reactions to drugs. *Lancet*. 2017; 390(10106):1996-2011.
28. Huisse MG, Pease S, Hurtado-Nedelec M, et al. Leukocyte activation: the link between inflammation and coagulation during heatstroke. A study of patients during the 2003 heat wave in Paris. *Crit Care Med*. 2008;36(8):2288-2295.
29. van der Poll T, de Jonge E, Levi M. Regulatory role of cytokines in disseminated intravascular coagulation. *Semin Thromb Hemost*. 2001;27(6):639-651.
30. Lavrentieva A, Kontakiotis T, Bitzani M, et al. Early coagulation disorders after severe burn injury: impact on mortality. *Intensive Care Med*. 2008;34(4):700-706.
31. Gando S. Disseminated intravascular coagulation in trauma patients. *Semin Thromb Hemost*. 2001;27(6):585-592.
32. Faye O, Wechsler J, Roujeau JC. Cell-mediated immunologic mechanism and severity of TEN. *Arch Dermatol*. 2005;141(6): 775-776.
33. Iqbal O, Syed D, Mosier M, et al. Immune-mediated activation of coagulation in patients with Stevens-Johnson syndrome/ toxic epidermal necrolysis. *Blood*. 2013;122(21):1117.
34. Walborn A, Hoppensteadt D, Syed D, Mosier M, Fareed J. Biomarker profile of sepsis-associated coagulopathy using biochip assay for inflammatory cytokines. *Clin Appl Thromb Hemost*. 2018;24(4):625-632.
35. Wada H, Thachil J, Di Nisio M, et al. Guidance for diagnosis and treatment of DIC from harmonization of the recommendations from three guidelines. *J Thromb Haemost*. 2013;11(4): 761-767.
36. Revuz J, Penso D, Roujeau JC, et al. Toxic epidermal necrolysis. Clinical findings and prognosis factors in 87 patients. *Arch Dermatol*. 1987;123(9):1160-1165.
37. Koh HK, Chai ZT, Tay HW, et al. Risk factors and diagnostic markers of bacteremia in Stevens-Johnson syndrome and toxic epidermal necrolysis: a cohort study of 176 patients. *J Am Acad Dermatol*. 2019;81(3):686-693.
38. Hunt BJ. Bleeding and coagulopathies in critical care. *N Engl J Med*. 2014;370(9):847-859.
39. Roujeau JC, Kelly JP, Naldi L, et al. Medication use and the risk of Stevens-Johnson syndrome or toxic epidermal necrolysis. *N Engl J Med*. 1995;333(24):1600-1607.
40. Mockenhaupt M, Viboud C, Dunant A, et al. Stevens-Johnson syndrome and toxic epidermal necrolysis: assessment of medication risks with emphasis on recently marketed drugs. The EuroSCAR-study. *J Invest Dermatol*. 2008;128(1):35-44.
41. Creamer D, Walsh SA, Dziewulski P, et al. U.K. guidelines for the management of Stevens-Johnson syndrome/toxic epidermal necrolysis in adults 2016. *Br J Dermatol*. 2016; 174(6):1194-1227.
42. Lin YF, Yang CH, Sindy H, et al. Severe cutaneous adverse reactions related to systemic antibiotics. *Clin Infect Dis*. 2014; 58(10):1377-1385.
43. Wang Q, Tian XB, Liu W, Zhang LX. Procalcitonin as a diagnostic indicator for systemic bacterial infections in patients with Stevens-Johnson syndrome/toxic epidermal necrolysis. *J Dermatol*. 2018;45(8):989-993.
44. Sfia M, Boeckler P, Lipsker D. High procalcitonin levels in patients with severe drug reactions. *Arch Dermatol*. 2007; 143(12):1591.
45. Jacobsen AA, Pearson DR. The age of procalcitonin: potential pitfalls in critically ill patients with SJS/TEN. A reply to ''Risk factors and diagnostic markers of bacteremia in Stevens-Johnson syndrome and toxic epidermal necrolysis: a cohort study of 176 patients''. *J Am Acad Dermatol*. 2020;82(6):e247.
46. Baron EJ, Miller JM, Weinstein MP, et al. A guide to utilization of the microbiology laboratory for diagnosis of infectious diseases: 2013 recommendations by the Infectious Diseases Society of America (IDSA) and the American Society for Microbiology (ASM)(a). *Clin Infect Dis*. 2013;57(4):e22-e121.
47. Levi M, Toh CH, Thachil J, Watson HG. Guidelines for the diagnosis and management of disseminated intravascular coagulation. British Committee for Standards in Haematology. *Br J Haematol*. 2009;145(1):24-33.
48. Roujeau JC, Chosidow O, Saiag P, Guillaume JC. Toxic epidermal necrolysis (Lyell syndrome). *J Am Acad Dermatol*. 1990;23(6 pt 1):1039-1058.
49. Su SC, Chung WH. Cytotoxic proteins and therapeutic targets in severe cutaneous adverse reactions. *Toxins (Basel)*. 2014; 6(1):194-210.
50. Yamazaki M, Aoshima K, Mizutani T, et al. Prednisolone inhibits endotoxin-induced disseminated intravascular coagulation and improves mortality in rats: importance of inflammatory cytokine suppression. *Blood Coagul Fibrinolysis*. 1999;10(6): 321-330.
51. Dodiuk-Gad RP, Chung WH, Yang CH, Lu CW, Hui RC, Shear NH. The 8th International Congress on Cutaneous Adverse Drug Reactions, Taiwan, 2013: focus on severe cutaneous adverse reactions. *Drug Saf*. 2014;37(6):459-464.
52. Lee HY, Dunant A, Sekula P, et al. The role of prior corticosteroid use on the clinical course of Stevens-Johnson syndrome and toxic epidermal necrolysis: a case-control analysis of patients selected from the multinational EuroSCAR and RegiSCAR studies. *Br J Dermatol*. 2012;167(3):555-562.
53. Law EH, Leung M. Corticosteroids in Stevens-Johnson syndrome/toxic epidermal necrolysis: current evidence and implications for future research. *Ann Pharmacother*. 2015;49(3): 335-342.
54. González-Herrada C, Rodríguez-Martín S, Cachafeiro L, et al. Cyclosporine use in epidermal necrolysis is associated with an important mortality reduction: evidence from three different approaches. *J Invest Dermatol*. 2017;137(10):2092-2100.
55. Paradisi A, Abeni D, Bergamo F, Ricci F, Didona D, Didona B. Etanercept therapy for toxic epidermal necrolysis. *J Am Acad Dermatol*. 2014;71(2):278-283.
56. Wang CW, Yang LY, Chen CB, et al. Randomized, controlled trial of TNF-alpha antagonist in CTL-mediated severe cutaneous adverse reactions. *J Clin Invest*. 2018;128(3):985-996.