Risk factors and mortality among patients with severe muco-cutaneous drug reactions

Anne-Mette Torp Crüger[1], Diljit Kaur-Knudsen[2], Claus Zachariae[2], Henrik Berg Rasmussen[3] & Simon Francis Thomsen[1]

ABSTRACT

INTRODUCTION: The aim of this study was to examine risk factors and mortality among patients with erythema multiforme (EM), Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN).

METHODS: This was a retrospective evaluation of the medical records of 250 patients from two Danish tertiary dermatological departments during a ten-year period.

RESULTS: In a total of 192 cases (77.4%), the primary diagnosis of EM (66.5%), SJS (62.2%) and TEN (100%) was confirmed, whereas the remaining cases (22.6%) were diagnosed differently. Antibiotics and allopurinol were predominantly associated with TEN, whereas SJS was associated with a broad spectrum of drugs. EM was related mainly to viral infections, predominantly herpes (30.6%); 38.2% of the causes of EM remained unknown. Patients with TEN had the highest mortality; i.e. 60% in the course of the ten-year study period: adjusted hazard ratio (HR) = 11.2 (95% confidence interval (CI): 3.65-34.35); p < 0.001 compared with EM patients. The risk of death was also increased among patients with SJS relative to patients with EM: HR = 2.60 (95% CI: 1.10-6.16); p = 0.030; however, this did not remain statistically significant after adjustment for age, co-morbidity, infection, cancer and polypharmacy, HR = 0.99 (95% CI: 0.38-2.57); p = 0.976.

CONCLUSIONS: We validated diagnoses in 250 patients with EM, SJS and TEN diagnosed during a ten-year period. The survival of patients with TEN was expectedly low compared with patients with EM. We extend previous findings by showing that after adjustment for confounders, the survival rates of SJS and EM are comparable.

FUNDING: not relevant.

TRIAL REGISTRATION: not relevant.

Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) are two rare, acute and potentially fatal muco-cutaneous skin diseases. The conditions are predominantly elicited by medications and share aetiology, pathogenesis and histological characteristics [1]. TEN and SJS differ in the extent of the affected total body surface area (TBSA). However, this distinction is arbitrary: SJS affects less than 10% of TBSA, whereas TEN affects more than 30% of TBSA. Patients with an affected TBSA in the 10-30% range have the SJS-TEN overlap syndrome [2]. The prognosis worsens with the size of the affected TBSA [3].

Erythema multiforme (EM) is mostly seen in patients with infections such as herpes simplex virus or *Mycoplasma pneumoniae* causing characteristic target-shaped eruptions of the skin. It is generally acknowledged that EM constitutes a separate and less severe disease due to its limited mucous membrane and epicutaneous involvement, and because risk factors only seem to overlap slightly with SJS and TEN [1].

We validated diagnoses in 250 patients diagnosed with TEN, SJS, or EM in two Danish tertiary dermatological departments in the course of a ten-year period and investigated the risk factors and mortality of these conditions.

METHODS

Selection procedure

We retrieved the medical records of all patients (n = 250) who were diagnosed (based on the 10th revision of the International Statistical Classification of Diseases and Related Health Problems, ICD-10; diagnosis codes: L51.0, L51.1, L51.2, L51.8, L51.9) with EM (n = 203), SJS (n = 37) or TEN (n = 8) in two university departments of dermatology in Copenhagen, Denmark, (Bispebjerg Hospital (n = 193) and Gentofte Hospital (n = 57)) in the period from January 2001 to December 2010. In total, 248 cases were included in the study as two EM patients with temporary personal identification numbers were excluded due to inaccessible medical records. The Danish Data Protection Agency (GEH-2011-057) and the Danish Health and Medicines Authority (3-3013-836/1/) approved the study.

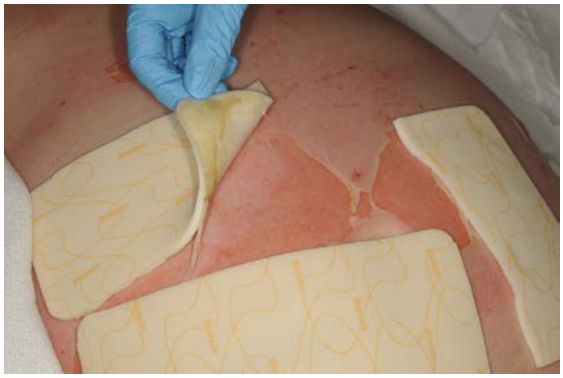
Data processing

The medical records of the 248 included cases were carefully examined by two authors, and 19 parameters were defined and collected in a database: date of birth, sex, primary diagnosis, possible causes of the skin eruption, date of diagnosis, date of death or emigration from Denmark (lost to follow-up), systemic infection, medical co-morbidities, polypharmacy (concurrent use of ≥ 5 systemic medications) [4], smoking, alcohol and/or illicit drug abuse (current or former), histopathology (result of

ORIGINAL ARTICLE

1) Department of Dermatology, Bispebjerg Hospital
2) Department of Dermato-allergology, Gentofte Hospital
3) Institute of Biological Psychiatry, Mental Health Centre Sct. Hans, Denmark

Dan Med J 2015;62(8):A5122



Toxic epidermal necrolysis with extensive epidermal detachment.

skin biopsy), epidermal destruction (positive Nikolsky´s sign or epidermal detachment), bullous eruption, mucous membrane affection (mouth, nasal, conjunctival and/or ano-genital), cancer (current or former), ethnicity, HIV/AIDS status, and a final conclusive diagnosis made by the research group based on re-evaluation of the medical records using the SCAR Consortium classification [5]. This classification recognises that mucous membrane erosions can be present in EM as well as in SJS and TEN, but that the individual pattern and distribution of the skin lesions differ. Particularly, EM is characterised by acrally distributed typical target lesions or raised atypical targets, whereas patients with SJS or TEN have more widespread flat skin lesions consisting of blisters arising on erythematous or purpuric macules. Implicit to this classification are the hypotheses that EM is different from SJS, and that SJS and TEN are only severity variants of a single entity.

TABLE 1

Demographic and clinical characteristics of 192 patients diagnosed with erythema multiforme, Stevens-Johnson syndrome and toxic epidermal necrolysis.

	EM (n = 144)	SJS (n = 38)	TEN (n = 10)	Total (N = 192)	p-value[a]
Age, mean, yrs[b]	39.8	52.4	62.9	43.5	< 0.001
Males, %	40.3	52.6	40.0	42.7	0.385
Co-morbidity, %	28.5	57.9	90.0	37.5	< 0.001
Infection, %	8.3	15.8	50.0	12.0	< 0.001
Smoking, %	33.3	29.4	28.6	32.0	0.936
Alcohol/illicit drug abuse, %	25.0	31.6	50.0	28.7	0.325
Cancer, %	8.3	26.3	20.0	12.5	0.009
Polypharmacy, %	9.7	29.7	70.0	16.8	< 0.001
Mucus membrane involvement, %	32.6	78.9	40.0	42.2	< 0.001
Bullae, %	29.9	39.5	80.0	34.4	0.004
Epidermal detachment, %	1.4	18.4	100	9.9	< 0.001
Non-Caucasian ethnicity, %	5.6	7.9	0	5.7	0.623
HIV-positive, %	1.4	2.6	0	1.6	0.791

EM = erythema multiforme; SJS = Stevens-Johnson syndrome; TEN = toxic epidermal necrolysis.
a) Test for overall difference between groups.
b) Calculated from available data.

Statistical analysis

The unpaired t-test and the chi-squared test were used to calculate differences in characteristics between the groups. The log-rank test was used to compare survival distributions between the groups. Factors associated with fatality were determined with a Cox proportional hazards regression model with time to death since diagnosis as the underlying time period. Covariates were final diagnosis, age, co-morbidity, infection, cancer and polypharmacy. Analyses were performed in SPSS 16.0 (SPSS, Inc., Chicago, IL).

Trial registration: not relevant.

RESULTS

In a total of 192 of the 248 cases (77.4%), the primary diagnosis of EM (66.5%), SJS (62.2%) and TEN (100%) was confirmed, whereas the remaining 56 cases (22.6%) were diagnosed differently when assessed based on retrospective examination of the medical records. These patients were either misdiagnosed within the disease spectrum (26 cases = 10.5%) or had other dermatoses associated with drug intake such as eczema, urticaria and bullous diseases (30 cases = 12.1%). In 41 of these 56 patients, the histological diagnosis was incompatible with EM, SJS and TEN, whereas one patient who was finally diagnosed with aphthous stomatitis had a biopsy result compatible with EM. A total of 14 of the 56 cases had no biopsy taken.

The patients with TEN were older (mean age: TEN = 62.9, range: 44-77 years; SJS = 52.4, range: 3-81 years; and EM = 39.8, range: 0-96 years) and had more co-morbidities (90%) than the patients with SJS (57.9%) and EM (28.5%) at the time of diagnosis (**Table 1**). In total, 22 (15.3%) of the patients with EM were children (< 18 years of age), whereas two of the patients with SJS (5.3%) were children. None of the TEN patients were children. In addition, 90% of the cases with TEN, 29.7% of the SJS cases and 9.7% of the cases with EM used multiple (≥ 5) drugs concurrently. Available data concerning smoking, illicit drug use and alcohol intake were insufficient. Thus, the relationship between these parameters and EM, SJS and TEN was not clarified in this study. 12.5% of the 192 cases either had a history of cancer or were currently being treated for cancer: 8.3% of the EM cases, 26.3% of the SJS cases and 20% of the TEN cases.

The most likely causes of EM, SJS and TEN were many and differed widely (**Table 2**). Herpes simplex accounted for 30.6% of the causes of EM, while 38.2% of the causes of EM were unknown. Of the 144 patients with EM, 47 (32.6%) had mucous membrane (predominantly lips) involvement. In all, 46.8% of the EM cases with mucous membrane involvement could be linked to

herpes infection, whereas only 22.7% of the EM cases without mucous membrane involvement were associated with herpes infection; the p-value for difference between groups was 0.003. Based on evaluation of the described temporal relationship between drug intake and symptom debut, TEN was associated predominately with antibiotics (five of ten cases). The SJS cases represented a broad spectrum of causes ranging from allopurinol (three of 38 cases) to antifungals (three of 38 cases), and with four unknown causes.

The patients with TEN had the highest ten-year mortality with a survival fraction of only 40% (**Figure 1**). Mortality among TEN patients was observed predominantly during the first weeks after diagnosis and all deaths in this group occurred within three months after diagnosis. This corresponded to an almost 15-fold increased risk of death in TEN cases relative to EM cases, hazard ratio (HR) = 14.81 (95% confidence interval (CI): 5.66-38.76); p < 0.001 (**Table 3**). This increased risk remained statistically significant also after adjustment for age, co-morbidity, infection, cancer and polypharmacy (adjusted HR = 11.2 (95% CI: 3.65-34.35); p < 0.001). The risk of death was also increased among patients with SJS relative to patients with EM: HR = 2.60 (95% CI: 1.10-6.16); p = 0.030. However, this did not remain statistically significant after adjustment for age, co-morbidity, infection, cancer and polypharmacy, HR = 0.99 (95% CI: 0.38-2.57); p = 0.976.

DISCUSSION

Retrospective validation of hospital records showed that around one fourth of all patients diagnosed with TEN, SJS and EM were later deemed to have been misclassi-

FIGURE 1

Mortality in 192 patients with erythema multiforme (EM), Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN).

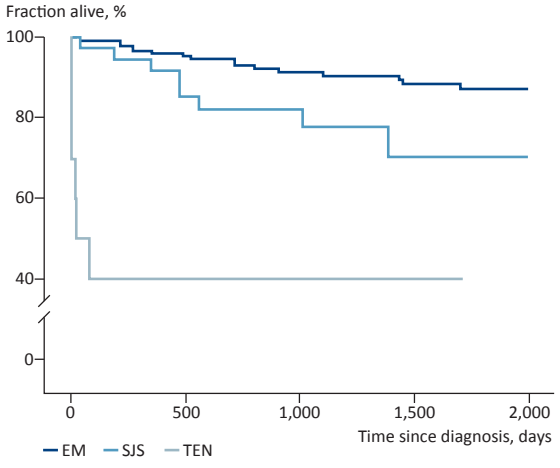


TABLE 2

Suspected causes of erythema multiforme, Stevens-Johnson syndrome and toxic epidermal necrolysis. The values are n (%).

	EM (n = 144)	SJS (n = 38)	TEN (n = 10)	Total (N = 192)
Drugs				
Antibiotics:	5 (3.5)	11 (28.9)	5 (50.0)	21 (10.9)
Amoxicillin	1 (0.7)	1 (2.6)[a]	0	2 (1.0)
Fluoroquinolones (ciprofloxacin)	1 (0.7)	1 (2.6)	0	2 (1.0)
Nitrofurantoin	0	1 (2.6)	0	1 (0.5)
Metronidazole	0	1 (2.6)	0	1 (0.5)
Penicillin	0	3 (7.9)	1 (10.0)	4 (2.1)
Cephalosporine (cefuroxime)	0	0	3 (30.0)	3 (1.6)
Sulphonamides	1 (0.7)	1 (2.6)	0	2 (1.0)
Trimethoprim	2 (1.4)	0	0	2 (1.0)
Sulphonamide + trimethoprim	0	2 (5.3)	0	2 (1.0)
Unknown antibiotics	0	1 (2.6)	1 (10.0)	2 (1.0)
Gastrointestinal drugs:	1 (0.7)	2 (5.3)	1 (10.0)	4 (1.0)
Pantoprazole, lansoprazole	1 (0.7)	2 (5.3)[b]	1 (10.0)	4 (1.0)
Analgesics:	1 (0.7)	2 (5.3)	0	3 (1.6)
Ibuprofen and paracetamol	1 (0.7)	0	0	1 (0.5)
Opioids (morphine and noscapine)	0	2 (5.3)	0	2 (1.0)
Cardiovascular drugs:	1 (0.7)	0	0	1 (0.5)
Beta-blockers (metoprolole)	1 (0.7)	0	0	1 (0.5)
CNS drugs:	2 (1.4)	7 (18.4)	1 (10.0)	10 (5.2)
Anti-epileptics (lamotrigine, oxcarbazepine, carbamazepine)	2 (1.4)	6 (15.8)	0	8 (4.2)
Antipsychotics (quetiapine)	0	1 (2.6)	0	1 (0.5)
Benzodiazepines (chlordiazepoxide)	0	0	1 (10.0)	1 (0.5)
SSRIs (citalopram)	1 (0.7)	0	0	1 (0.5)
Immunomodulatory drugs:	1 (0.7)	2 (5.3)	1 (10.0)	4 (2.1)
Antimetabolites (azathioprine, gemcitabine)	1 (0.7)	0	1 (10.0)	2 (1.0)
Sulfasalazine	0	1 (2.6)	0	1 (0.5)
Protein kinase inhibitors (imatinib)	0	1 (2.6)	0	1 (0.5)
Antimycotics (fluconazole, terbinafine, voriconazole)	1 (0.7)	3 (7.9)	0	4 (2.1)
Antimalarials (hydroxychlorochine)	0	1 (2.6)	0	1 (0.5)
Allopurinol	0	3 (7.9)	2 (10.0)[c]	5 (2.6)
Aromatase inhibitors (anastrozole)	0	1 (2.6)	0	1 (0.5)
Antithyroid drugs (thiamazole)	0	1 (2.6)	0	1 (0.5)
Other drugs	3	1 (2.6)	0	4 (2.1)
Infections				
Mycoplasma pneumoniae	4 (2.8)	0	0	4 (2.1)
Other respiratory tract infections	4 (2.8)	0	0	4 (2.1)
Viral infection:	45 (31.3)	0	0	45 (23.4)
Herpes simplex	44 (30.6)	0	0	44 (22.9)
Epstein Barr virus	1 (0.7)	0	0	1 (0.5)
Other unknown infections	15 (10.4)	0	0	15 (7.8)
Other causes				
Radiocontrast agents	1 (0.7)	0	0	1 (0.5)
Keratolytics	1 (0.7)	0	0	1 (0.5)
Vaccines (pneumococcal)	1 (0.7)	0	0	1 (0.5)
Sarcoidosis	1 (0.7)	0	0	1 (0.5)
Scabies	1 (0.7)	0	0	1 (0.5)
Unknown	55 (38.2)	4 (10.5)	0	59 (30.7)

CNS = central nervous system; EM = erythema multiforme; SJS = Stevens-Johnson syndrome; SSRI = selective serotonin re-uptake inhibitors; TEN = toxic epidermal necrolysis.
a) Or lamotrigine.
b) Or 1 case caused by sildenafil.
c) Or 1 case caused by colcichine.

TABLE 3

Predictors of survival among 192 patients with erythema multiforme, Stevens-Johnson syndrome and toxic epidermal necrolysis.

	Crude		Adjusted	
	HR (95% CI)	p-value	HR (95% CI)	p-value
Disease type		< 0.001		< 0.001
EM	1.00 (ref.)	–	1.00 (ref.)	–
SJS	2.60 (1.10-6.16)	0.030	0.99 (0.38-2.57)	0.976
TEN	14.81 (5.66-38.76)	< 0.001	11.20 (3.65-34.35)	< 0.001
Age[a]	2.31 (1.78-3.01)	< 0.001	2.02 (1.39-2.95)	< 0.001
Co-morbidity	5.63 (2.49-12.75)	< 0.001	2.09 (0.83-5.27)	0.118
Infection	2.01 (0.82-4.94)	0.128	1.08 (0.41-2.85)	0.869
Cancer	8.17 (3.89-17.16)	< 0.001	6.58 (2.65-16.32)	< 0.001
Polypharmacy	7.41 (3.53-15.57)	< 0.001	1.94 (0.80-4.67)	0.142

CI = confidence interval; EM = erythema multiforme; HR = hazard ratio; SJS = Stevens-Johnson syndrome; TEN = toxic epidermal necrolysis.
a) Per 10 yrs.

fied. Known and suspected causative drugs were found to be related to TEN and SJS, whereas EM was shown to be predominantly associated with infections such as herpes, and less frequently with medications. Approximately one third of EM patients had mucous membrane involvement. Among these, almost half were suspected to have been caused by herpes compared with only one fourth of the cases of EM without mucous membrane involvement.

The survival of patients with SJS, but particularly with TEN, was expectedly low compared with that of patients with EM. We extend previous findings by showing that after adjustment for age, co-morbidities, polypharmacy and cancer, the survival rates of SJS and EM were comparable.

Evaluation of study quality

The accessibility of information regarding the parameters of most interest for this study was high. Only two of the 250 cases were excluded due to inaccessible medical records. A limitation of the study was its retrospective design based on examination of historical patient records. This implies that even after careful evaluation of the descriptions in the patient records, a definite culprit drug cannot be identified, particularly for patients with TEN in whom polypharmacy is common. Epidermal detachment was described as either generalised or localised in the medical records. The exact TBSA was described only in a few cases, which made it impossible to identify the SJS-TEN overlap syndrome. Unfortunately, screening for herpes simplex and *M. pneumoniae* was not systematic, which is a limitation of the study. Also, the available data did not allow for calculation of a severity of illness score such as SCORTEN [3], which would have been interesting.

Dissociation between initial and final diagnosis

We observed a considerable difference between the first registered and the final diagnosis in patients with EM, SJS and TEN in this consecutive ten-year sample. Some of the cases had received the primary diagnosis SJS and were then later revised to EM, and vice versa. One third of the initial cases diagnosed with EM either belonged to a broad spectrum of other diseases with a similar symptomatology or were SJS or TEN. SJS showed a similar pattern except for a few cases that were finally diagnosed with other diseases. In contrast, all initial cases of TEN were also finally diagnosed with TEN. Two of the final TEN cases were initially diagnosed as EM and SJS. We suggest that these findings are the consequence of an historical lack of consensus concerning the terminology of the three skin diseases and their diagnoses [1].

Risk factors and mortality

In line with existing knowledge, we found that certain drugs are more likely to elicit TEN and SJS. Notably, a case-control study with data obtained through surveillance networks in France, Germany, Italy and Portugal found that sulphonamides had the strongest association with development of SJS and TEN with a crude relative risk of these disorders of 172 [6]. Trimethoprim-sulfamethoxazole accounted for 69% of the SJS and TEN cases in that study, with a median relative-risk estimate of 160, whereas cephalosporins had a multivariate relative risk of SJS or TEN of 14 [6]. The multivariate relative risk of SJS or TEN due to allopurinol was 5.5. Additionally, anticonvulsants, oxicam non-steroidal anti-inflammatory drugs, chlor-mezanone and corticosteroids were associated with the development of SJS and TEN.

In our study, sulphonamides alone accounted for only one case of TEN (10%), no cases of SJS and one case of EM (0.7%). The combination of sulphonamides and trimethoprim caused only two cases of SJS (5.3%) and trimethoprim alone caused two cases of EM (1.4%). In contrast, antibiotics were responsible for as many as 50% of the TEN cases with cephalosporins being the dominant antibiotic causing three of the TEN cases (30%), but none of the EM or SJS cases. Allopurinol caused three cases of SJS (7.3%) and one case of TEN (10%). Except for four cases caused by viral infection and four cases with unknown causes, drugs were responsible for SJS in our sample. EM was predominately caused by herpes and other infections and occasionally by drugs, primarily antibiotics. In total, 55 (38.2%) of the EM cases had unknown causes.

The mortality rate of TEN in the ten-year study period was 60%, and mortality among TEN patients was confined primarily to the weeks immediately following diagnosis. Also, SJS patients had a poorer survival than EM patients, but this was shown to be due to a higher

mean age and more co-morbidities including cancer, among patients with SJS. When adjusting for these confounders, there was no significant difference in survival between the EM group and the SJS group. Because severe adverse cutaneous drug reactions are very rare, knowledge of mortality is derived mainly from case reports or small patient series [7, 8]. However, a recent very comprehensive (and to date the largest study of prognosis of SJS and TEN, n = 460) of Europeans selected from the RegiSCAR cohort found one-year mortality rates of 24% for SJS, 43% for SJS-TEN overlap and 49% for TEN [9]. These estimates seem to fit well with our mortality estimate for TEN, but to be much higher for SJS. Also, in contrast to our findings, a small five-year retrospective study from Singapore observed no deaths among five patients with TEN [10].

Furthermore, a study of 35 adult patients with TEN from a burn unit in Canada showed that a little less than 30% died in hospital shortly after diagnosis [11]. This is in accordance with a retrospective study of 64 patients with TEN treated in a burn unit in the United States, which also found a mortality rate of close to 30% [12]. Finally, another study from a burn unit in the United States found a mortality rate of around 35% among 36 patients with TEN [13]. The somewhat higher mortality observed in our cohort for TEN may be due to a higher age and a high occurrence of co-morbidities in these patients compared with previous studies. Also, our patients may have had more severe TEN.

Finally, we have to acknowledge that we only identified ten patients with TEN meaning that representativeness is probably not secured in the present study.

CONCLUSIONS

We validated diagnoses in 248 patients with EM, SJS and TEN diagnosed in the course of a ten-year period. The survival of patients with TEN was expectedly low compared with patients with EM. We extend previous findings by showing that after adjustment for confounders, the survival rates of SJS and EM are comparable.

CORRESPONDENCE: *Simon Francis Thomsen*, Dermato-venerologisk Afdeling D, Bispebjerg Hospital, Bispebjerg Bakke 23, 2400 Copenhagen NV, Denmark. E-mail: simonfrancisthomsen@gmail.com

ACCEPTED: 2 June 2015

CONFLICTS OF INTEREST: none. Disclosure forms provided by the authors are available with the full text of this article at www.danmedj.dk

LITERATURE

1. Lissia M, Mulas P, Bulla A et al. Toxic epidermal necrolysis (Lyell's disease). Burns 2010;36:152-63.
2. Bastuji-Garin S, Rzany B, Stern RS et al. Clinical classification of cases of toxic epidermal necrolysis, Stevens-Johnson syndrome, and erythema multiforme. Arch Dermatol 1993;129:92-6.
3. Bastuji-Garin S, Fouchard N, Bertocchi M et al. SCORTEN: a severity-of-illness score for toxic epidermal necrolysis. J Invest Dermatol 2000;115:149-53.
4. Linjakumpu T, Hartikainen S, Klaukka T et al. Use of medications and polypharmacy are increasing among the elderly. J Clin Epidemiol 2002;55:809-17.
5. Auquier-Dunant A, Mockenhaupt M, Naldi L et al. Severe cutaneous adverse reactions. 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;138:1019-24.
6. 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; 333:1600-7.
7. Breathnach SM. Erythema multiforme, Stevens-Johnson syndrome and toxic epidermal necrolysis. In: Burn T, Breathnach S, Cox N et al, eds. Rook's Textbook of Dermatology. Oxford: Wiley-Blackwell, 2010:76.1-22.
8. Harr T, French LE. Toxic epidermal necrolysis and Stevens-Johnson syndrome. Orphanet J Rare Dis 2010;5:39.
9. Sekula P, Dunant A, Mockenhaupt M et al. Comprehensive survival analysis of a cohort of patients with Stevens-Johnson syndrome and toxic epidermal necrolysis. J Invest Dermatol 2013;133:1197-204.
10. Su P, Aw CW. Severe cutaneous adverse reactions in a local hospital setting: a 5-year retrospective study. Int J Dermatol 2014;53:1339-45.
11. Haber J, Hopman W, Gomez M et al. Late outcomes in adult survivors of toxic epidermal necrolysis after treatment in a burn center. J Burn Care Rehabil 2005;26:33-41.
12. Oplatek A, Brown K, Sen S et al. Long-term follow-up of patients treated for toxic epidermal necrolysis. J Burn Care Res 2006;27:26-33.
13. Ducic I, Shalom A, Rising W et al. Outcome of patients with toxic epidermal necrolysis syndrome revisited. Plast Reconstr Surg 2002;110:768-73.