Etiologies and effect of systemic corticosteroids on the outcome of Stevens Johnson syndrome, Toxic Epidermal Necrolysis and Erythema Multiforme in Ramathibodi Hospital.

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ABSTRACT:

SAHAWATWONG S*, RAJATANAVIN N. ETOLOGIES AND EFFECT OF SYSTEMIC CORTICOSTEROIDS ON THE OUTCOME OF STEVENS JOHNSON SYNDROME, TOXIC EPIDERMAL NECROLYSIS AND ERYTHEMA MULTIFORME IN RAMATHIBODI HOSPITAL. THAI J DERMATOL 2016; 32: 93-105.**

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Background: : Toxic epidermal necrolysis (TEN), Stevens-Johnson syndrome (SJS) and Erythema multiforme (EM) are immune-complex–mediated hypersensitivity reaction to drugs and certain infection with high mortality and morbidity. To date, no sufficient evidence of any benefit from specific treatment was shown.

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Objectives: To evaluate etiologies and association between treatment outcome and systemic corticosteroids in Toxic epidermal necrolysis (TEN), Stevens-Johnson syndrome (SJS) and Erythema multiforme (EM).

Methods: Retrospective reviewed of the SJS, overlapping SJS/TEN, TEN and EM patients admitted to Ramathibodi Hospital from January 2002 to October 2009.

Results: There were 87 cases which consisted of 15 TEN patients (17.2%), 9 SJS/TEN patients (10.3%), 52 SJS patients (59.8%) and 11 EM patients (12.6%). Further analysis was performed in severe cutaneous reaction group (SJS, SJS/TEN and TEN patients). The 3 most common causative drugs were carbamazepine(11%), co-trimoxazole(9%) and allopurinol(8%) respectively. In addition to cessation of culprit drug and supportive care, systemic corticosteroids, either with or without intravenous immunoglobulin(IVIG), were given to 72% of patients. The mortality rate was 13.15%, which occurred in 3, 4 and 3 cases of TEN, overlapping SJS/TEN and SJS respectively. The patients who received systemic corticosteroids without IVIg had superior survival than those who received supportive treatment only. There was no significant association between systemic corticosteroids and prolonged hospitalization. The correlation between systemic corticosteroids and infection rate was inconclusive.

Conclusion: SJS, overlapping SJS/TEN and TEN are mainly caused by drugs and lead to high mortality and morbidity rate. Our study show that systemic corticosteroids may have positive effects on these life-threatening dermatologic conditions.

Key word: Corticosteroids, Stevens-Johnson syndrome, Toxic epidermal necrolysis

บทคัดย่อ:

สินิชญาน์ สหวัฒน์วงศ์* ณัฏฐา รัชตะนาวิน การศึกษาสาเหตุ และประสิทธิผลของยาคอร์ติโคสเตียรอยด์ ในการรักษาผู้ป่วยกลุ่มอาการสตีเวนส์จอห์นสันและโรคทอกซิก อิพิเดอร์มัล เนโครไลซิส ในโรงพยาบาลรามาธิบดี วารสารโรคผิวหนัง 2559; 32: 93-105.**

แผนกผิวหนัง โรงพยาบาลสมิติเวช สุขุมวิท

หน่วยโรคผิวหนัง ภาควิชาอายุรศาสตร์ คณะแพทยศาสตร์โรงพยาบาลรามาธิบดีมหาวิทยาลัยมหิดล

หลักการและเหตุผล: กลุ่มอาการสตีเวนส์จอห์นสันและโรคทอกซิก อิพิเดอร์มัล เนโครไลซิสเป็นภาวะที่เกิดจากปฏิกิริยาของระบบภูมิคุ้มกันต่อยา หรือการติดเชื้อ ภาวะนี้มีความรุนแรงและอัตราการเสียชีวิตสูง ปัจจุบัน ไม่พบหลักฐานที่สนับสนุนประโยชน์ของการรักษาใดชัดเจน

วัตถุประสงค์: เพื่อศึกษาสาเหตุ และประสิทธิภาพการรักษาด้วยยาคอร์ติโคสเตียรอยด์ในผู้ป่วยกลุ่มอาการสตีเวนส์จอห์นสันและโรคทอกซิก อิพิเดอร์มัล เนโครไลซิส

วิธีการศึกษา: วิเคราะห์ข้อมูลย้อนหลังจากเวชระเบียนของผู้ป่วยกลุ่มอาการสตีเวนส์จอห์นสัน และโรคทอกซิก อิพิเดอร์มัล เนโครไลซิสที่ได้รับการรักษาแบบผู้ป่วยในของโรงพยาบาลรามาธิบดีระหว่างเดือนมกราคม พ.ศ. 2545 ถึงเดือนตุลาคม พ.ศ. 2552

ผลการศึกษา: ผู้ป่วยทั้งหมด 87 คนประกอบด้วยผู้ป่วยอรีทริมา มัลติฟอร์ม 11 คน(12.6%) สตีเว่น จอห์นสัน ซินโดรม 52 คน(59.8%) ภาวะก้ำกึ่งระหว่างสตีเว่น จอห์นสัน ซินโดรมกับทอกซิก อิพิเดอร์มัล เนโครไลซิส 9 คน(10.3%)และโรคทอกซิก อิพิเดอร์มัล เนโครไลซิส 15 คน(17.2%) เมื่อวิเคราะห์กลุ่มโรคที่เป็นปฏิกริยารุนแรง ได้แก่สตีเว่น จอห์นสัน ซินโดร ภาวะก้ำกึ่งระหว่างสตีเว่น จอห์นสัน ซินโดรมกับทอกซิก อิพิเดอร์มัล เนโครไลซิสและโรคทอกซิก อิพิเดอร์มัล เนโครไลซิส สาเหตุหลักเกิดมาจากยาและยาที่พบเป็นสาเหตุมากที่สุด 3 ชนิดคือ carbamazepine(11%) co-trimoxazole(9%) และallopurinol(8%)ตามลำดับ การรักษาหลักประกอบด้วยการหยุดยาที่เป็นสาเหตุร่วมกับการรักษาประคับประคอง นอกจากนี้ยังมีการใช้ยาคอร์ติโคสเตียรอยด์และอิมมูโนโกลบูลินร่วมด้วย อัตราการเสียชีวิตจากโรคคือ13.15% ซึ่งพบในผู้ป่วยสตีเว่น จอห์นสัน ซินโดรม 3 คน ภาวะก้ำกึ่งระหว่างสตีเว่น จอห์นสัน ซินโดรมกับทอกซิก อิพิเดอร์มัล เนโครไลซิส 4 คน และทอกซิก อิพิเดอร์มัล เนโครไลซิส 3 คน การศึกษาพบว่ากลุ่มผู้ป่วยที่ได้รับยาคอร์ติโคสเตียรอยด์โดยไม่ได้รับอิมมูโนโกลบูลินร่วมด้วยมีอัตราการรอดชีวิตสูงกว่ากลุ่มที่ได้รับการรักษาแบบประคับประคอง ไม่พบว่าการได้รับยาคอร์ติโคสเตียรอยด์เพิ่มระยะเวลาการรักษาตัวในโรงพยาบาล และไม่สามารถสรุปความสัมพันธ์ระหว่างยาคอร์ติโคสเตียรอยด์กับการติดเชื้อในกระแสเลือดได้.

สรุปผล: สตีเว่น จอห์นสัน ซินโดรม ภาวะก้ำกึ่งระหว่างสตีเว่น จอห์นสัน ซินโดรมกับทอกซิก อิพิเดอร์มัล-เนโครไลซิส และโรคทอกซิก อิพิเดอร์มัล เนโครไลซิสมีสาเหตุจากยาเป็นหลัก และมีอัตราการเสียชีวิตสูง ผลการศึกษานี้พบว่ายาคอร์ติโคสเตียรอยด์ช่วยลดอัตราการเสียชีวิต

คำสำคัญ: คอร์ติโคสเตียรอยด์, สตีเว่น จอห์นสัน ซินโดรม, โรคทอกซิก อิพิเดอร์มัล เนโครไลซิส, สาเหตุ

Background

Toxic epidermal necrolysis (TEN), Stevens-Johnson syndrome (SJS) and Erythema multiforme(EM) are immune-complex–mediated hypersensitivity reaction to drugs and certain infection. They are closely related and represent different severities of one disease spectrum. The most widely accepted classification by Bastuji-garin et al,[1] divided into 5 categories (1) Bullous erythema multiforme (EM): epidermal detachment involving<10% of the body surface, coupled with localized typical targets or raised atypical targets (2) SJS: epidermal detachment of<10% of the body surface in association with widespread erythematous or purpuric macules or flat atypical targets (3) SJS/TEN overlap: epidermal detachment of 10% to 30% of the body surface plus widespread purpuric macules or flat atypical targets (4) TEN with spots: epidermal detachment of>30% of the body surface coupled with widespread purpuric macules or flat atypical targets (5) TEN without spots: large sheets of epidermal

detachment involving> 10% of the body surface without purpuric macules or target lesions. EM is different from SJS and TEN in terms of clinical signs and precipitating factors. Herpes simplex virus (HSV) is clearly the most common associated infectious agent, with *Mycoplasma pneumonia* and other infectious pathogens (*Histoplasma capsulatum* and parapoxvirus (orf), etc.) are observed less frequently. More rarely, EM has been associated with drugs or systemic disease. SJS and TEN are rare but severe cutaneous adverse reactions (SCAR) related to a variety of medications.[2] More than 100 drugs have been associated with SJS/TEN, most often implicated are anti-epileptics, sulphonamides, β-lactam antibiotics, non-steroidal anti-inflammatory drugs and allopurinol.[3] The differential diagnosis for SJS and TEN includes staphylococcal scalded skin syndrome (SSSS), lupus-associated TEN, linear IgA dermatosis, paraneoplastic pemphigus, acute graft-versus-host disease, drug-induced pemphigoid and pemphigus, and acute generalized exanthematous pustulosis.[4] They have a significant public health impact because of high mortality and morbidity. The average reported mortality rate of SJS is 1-5%, and of TEN is 25-35%; it can be even higher in elderly patients and those with a large surface area of epidermal detachment.[5]

Apart from intensive supportive therapy, a generally accepted regimen for specific treatment of SJS/TEN is lacking. Because immunologic mechanism has been suspicious, treatment options such as systemic corticosteroids, intravenous immunoglobulin therapy (IVIG) and other immunosuppressive therapy had been applied. Among these systemic therapy, corticosteroids is one of the most widely used but its efficacy has been very controversial. Proponents emphasized the importance of early intervention during the initial erythrodermic stage, with high doses for a few days only, to inhibit inflammation. Opponents suggested an increased risk of sepsis, prolonged length of hospital stay, and increased mortality in TEN patients treated with corticosteroids.[6]

Objectives

To evaluate incidence and etiologies of EM, SJS, SJS-TEN overlap and TEN in Thai patients admitted to Ramathibodi Hospital. The association between treatment outcome and systemic corticosteroids focus on SJS, SJS-TEN overlap and TEN group was also evaluated.

Methods

This study was approved by the Ethical Committee on Human Rights Related to Researches Involving Human Subjects Faculty of Medicine, Ramathibodi hospital, Mahidol University. A retrospective analysis of the medical records of patient's admitted in Ramathibodi Hospital with diagnosis of EM, SJS, SJS-TEN overlap and TEN, from January 2002 to October 2009, was performed. Patient's age, sex, causative agent (culprit drugs, infection) were collected. The SCORTEN and time to reepithelization could not be completely collected due to insufficiency of the data. Association between treatment and outcome was tested

by Fisher's exact test and simple logistic regression analysis was use to calculate odd ratio. The comparison in terms of length of hospital stay was performed using Mann-Whitney U-test. Statistical significance was defined as $P < 0.05$. Statistical analyses were conducted using SPSS 16.0.

Results

There were 87 patients admitted with EM, SJS, SJS-TEN overlap and TEN from January 2002 to October 2009, SJS was the majority of the cases (59%) , followed by TEN (17%), EM (13%) and SJS-TEN overlap (11%), respectively (Table 1). According to difference in age group of patient, clinical course and etiology, we considered EM as a distinct disease apart from the three others (SJS, SJS-TEN overlap and TEN). For EM, almost three-quarters of them were children under 15 years-old and almost equal number on both genders. Median length of hospital stay for EM patients was 4 days. The prognosis of disease was excellent. There was neither severe complication nor death from the disease. While, for SJS, SJS-TEN overlap and TEN, the majority of patients were 16-70 years old. Overall, female patients predominated, except for TEN, which did not have gender difference. The mortality rate of SJS, SJS-TEN overlap and TEN was 5.8%, 40% and 20%, respectively. The Average mortality rate for all three diseases was 13%.

In term of etiologies, drugs were the most frequent cause of EM (Figure 1A). Viral infection, diagnosis was bared on DIF staining, accounted for almost 20%. For the other three diseases, dsugs was also the leading cause and responsible for almost 90% of cases (Figure1B). The distribution of culprit drugs for SJS, SJS-TEN overlap and TEN was shown in figure 2. Antimicrobial group was the most suspected causative agents, represented almost 50%, followed by 2 anticonvulsant drugs carbamazepine and phenytoin accounted for 11%, followed by trimethoprim-sulfamethoxazole (9%) and allopurinol (8%). List of culprit drugs were shown in Table 2

Treatment of EM and SJS/TEN was mainly supportive and symptomatic treatment. For SJS/TEN, supportive treatment was also a standard treatment. Other treatment modalities included systemic corticosteroids (intravenous dexamethasone, intravenous methylprednisolone and oral prednisolone), N-Acetyl Cysteine (NAC) and intravenous immunoglobulin (IVIG). We classified treatments of SJS/TEN into 3 main groups, 1) supportive treatment only, 2) supportive treatment plus systemic corticosteroids 3) supportive treatment plus systemic corticosteroids plus IVIG. Systemic corticosteroids was used early in the course of admission, 71.4% of cases within first 24 hr. The distribution of cases in each treatment group was shown in Figure 3. We analyzed outcome of systemic corticosteroids focusing on impact of mortality and hospital length of stay by compared treatment group2 (supportive treatment plus systemic corticosteroids) with treatment group1 (supportive treatment only) which was the control group. We

excluded 10 patients from the analysis, 4 patients in the third group of treatment (supportive treatment plus systemic corticosteroids plus IVIG) because of the limit number of cases and 6 patients who died from their underlying causes or unrelated events. Overall, there were 52 patients of supportive plus systemic corticosteroids-treatment group and 15 patients from supportive treatment group were analyzed. Patients in both groups showed similar characters in age, sex, underlying HIV infection and disease severity distribution (Table3). Patients who received supportive treatments plus systemic corticosteroids had statistically significant, higher survival rate. Univariate logistic regression analysis revealed odd ratio 6 with 95% confidence interval 1.36-2.38 (Table 4). There was no difference in length of hospital stay between patients who received supportive treatments plus systemic corticosteroids and patients who received supportive treatments only (*P* value = 0.241).

Table 1 The demographic data of all patients

	EM	**SJS**	**SJS/TEN**	**TEN**	**Overall**
Number of patients (%)	11 (13%)	51 (59%)	10 (11%)	15 (17%)	87
Age≤15	8 (73%)	10 (20%)	0	3 (20%)	21 (24%)
Age 16-40	0	18 (35%)	1 (10%)	7 (47%)	26 (30%)
Age 41-70	3 (27%)	17 (33%)	7(70%)	5 (33%)	32 (37%)
Age ≥71	0	6 (12%)	2 (20%)	0	8 (9%)
Median age (max-min)	13 (0.08-57)	37.5 (3-84)	47 (35-84)	36 (0.58-70)	38 (0.08-84)
M:F	6:5	23:29	3:6	8:7	38:49
Mortality rate (%)	0	3/51 5.8%	4/10 40%	3/15 20%	EM=0% SJS/TEN=13%

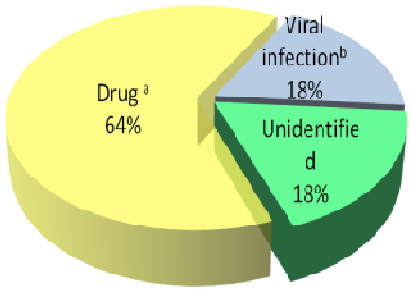


Figure 1A Cause of EM

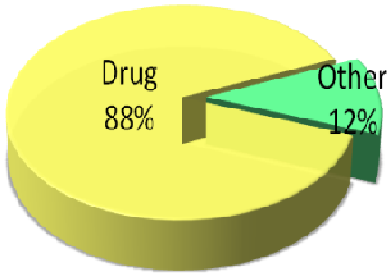
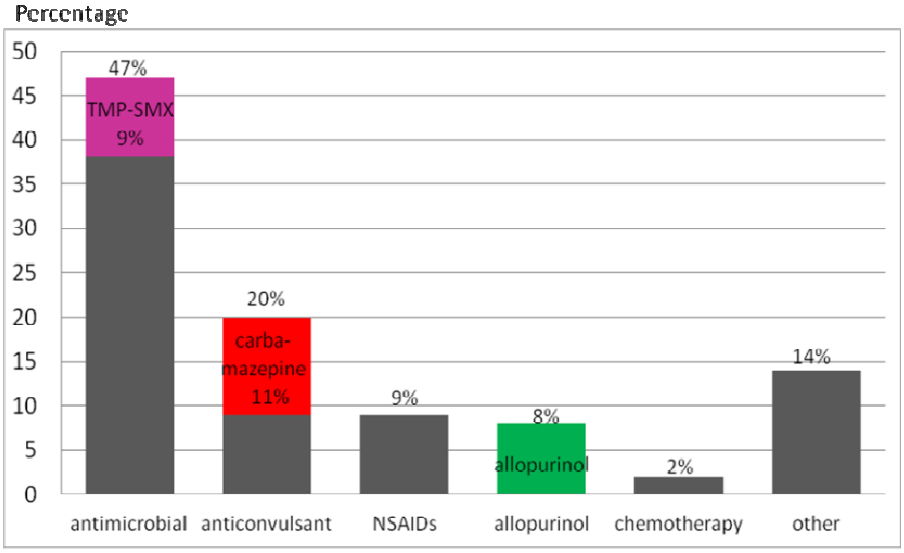


Figure 1B Cause of SJS, SJS-TEN overlap and TEN

[a]Drug : amoxicillin, penicillin, vancomycin, azithromycin, clindamycin, ibuprofen and Herbal medicine

[b]viral infection : herpes simplex virus and unidentified viral infection



TMP-SMX, trimethoprim-sulfamethoxazole

Figure 2 Distribution of culprit drugs for SJS, SJS-TEN overlap and TEN

Table 2 List of culprit drugs (alphabetical)

Culprit drugs in TEN patients	Culprit drugs in SJS/TEN patients	Culprit drugs in SJS patients
Allopurinol	Acetaminophen	Allopurinol
Carbamazepine	Allopurinol	Amoxycillin
Cephalosporin	Capecitabine	Carbamazepine
Ciprofloxacin	Contrast media	Colchicine
Nevirapine	Dicloxacillin	Ethambutol
NSAIDs	Docetaxel	NSAIDs
Phenytoin	Effavaren	Phenytoin
Pyrazinamide	Ibuprofen	TMP-SMX
Pyrimethamine	Phenytoin	
Sulfadiazine	Pseudoephridine	
TMP-SMX	TMP-SMX	

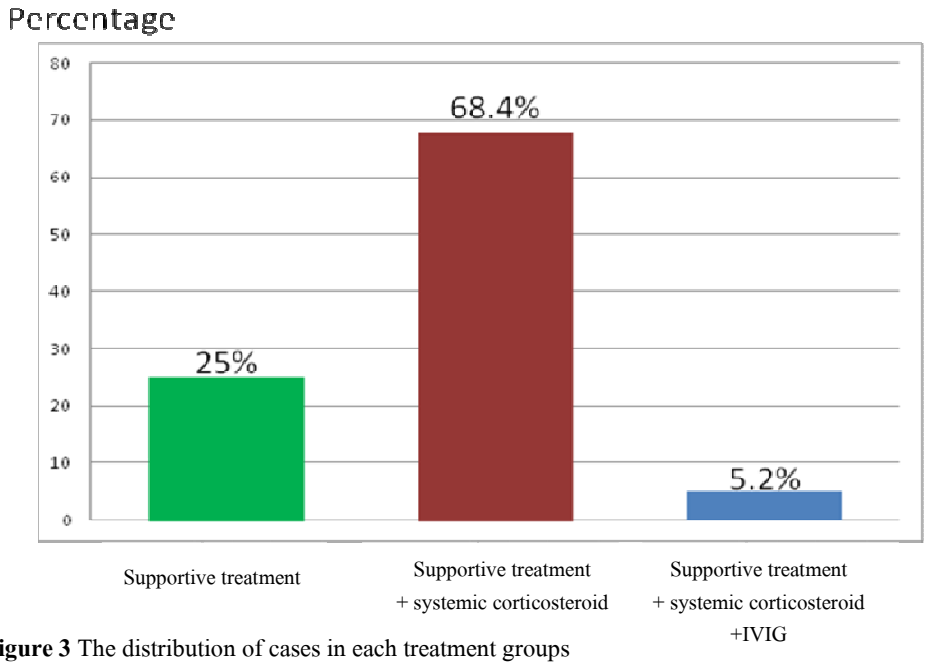


Figure 3 The distribution of cases in each treatment groups

Table 3 Characteristics of patients in supportive treatment group and supportive treatment + systemic corticosteroids

	Supportive treatment (Group1) (n = 15)	**Supportive treatment + Systemic corticosteroids (Group2) (n=52)**
Male:Female	1:1.5	1:1.2
Number of HIV positive patients	4 (27%)	11 (21%)
Number of patients		
SJS	9 (60%)	39 (75%)
SJS/TEN	2 (13%)	6 (12%)
TEN	4 (27%)	7 (13%)
Total	15	52
Median length of hospital stay (Min-Max)	7 (3-54) days	10 (2-63) days

Table 4 Comparison of survival between supportive treatment group and supportive treatment + systemic corticosteroids

	Treatments		
Outcome	**Supportive treatment** (Group1)	**Supportive treatment + Systemic corticosteroids** (Group2)	**Total**
Dead	5	4	9
	55.56%	44.44%	100%
Alive	10	48	58
	17.24%	82.76%	100%
Total	15	52	67
	22.39%	77.61%	100%

Fisher's exact test P value = 0.022, univariated logistic regression odd ratio = 6

Discussion

SJS was the most common diseases in our study. Erythema multiforme was a distinctive disease apart from SJS, SJS-TEN overlap and TEN because EM affected mainly younger age group, predominantly under 15 years and also had excellent outcome. There was no mortality and average length of hospital stay was relatively short (4 days). Regarding an etiology of EM, our study differed from previous study which infection was the cause in the majority[7]. We proposed hypothesis of the oversensitivity in diagnosis of drug induced cutaneous reaction in childhood patients. Infection may exhibit nonspecific clinical sign and symptoms which usually led to empirical antibiotic treatment. The subsequent development of cutaneous rash from infection might mislead physician to the diagnosis of drug induced EM. However, the drug induced disease in EM group was lower than SJS, SJS-TEN overlap and TEN group.

For Severe Cutaneous Adverse Reactions (SCARs); SJS, SJS-TEN, our data showed that the 3 most common suspected causative drugs were carbamazepine, trimethoprim-sulfamethoxazole and allopurinol, which accounted for 11%, 9% and 8% of all drugs, respectively. The EUROSCAR study, which was one of the world's largest population base analysis, demonstrated same 3 leading culprit drugs, although in different order.[9] The finding underscored the high potential of carbamazepine, trimethoprim-sulfamethoxazole and allopurinol in causing severe cutaneous adverse reactions. Fortunately, the risk of SJS, SJS-TEN overlap and TEN from carbamazepine and allopurinol could be reduced by screening a unique HLA , especially in Asian patients. Tassaneeyakul et al, showed a strong association in Thai population between the HLA-B*1502, SJS and carbamazepine[10]. This study also demonstrated high association with odds ratio (OR) of 54.76, 88.10%. sensitivity and specificity, 1.92% positive predictive value (PPV) and 99.96% negative predictive value. However the same genetic correlation could not be shown in Japanese, U.S. and Europeans. [11-13] For allopurinol, the risk of SJS/TEN was significantly greater in patients with HLA-B*5801 with an odds ratio of 348.3, 100% sensitivity and 87% specificity. This association also found in Japanese patients[11], and to a lesser extent, in patients of European origin[14]. Thus, HLA-B screening prior to administration of carbamazepine, allopurinol or other drugs which SCAR should be recommended after cost effectiveness analysis.

Although several systemic treatment protocols for TEN have been published, none has been formally established in a randomized controlled trial, and hence cannot definitively be proposed as a treatment regimen. Management requires early recognition and immediate withdrawal of any potential causative agents. Many patients took different drugs simultaneously preceding the onset of clinical symptoms. There are no reliable tests to demonstrate the link between a single case and a specific drug. The determination of the culprit drug

relies on clinical assumption, mainly based on the timing of the reaction. A mean time of 14 days from initial drug administration to the onset of TEN has been noted[15]. Moreover, the sensitizing properties of different drugs should be taken into account. In addition, fluid replacement, electrolyte balancing, nutritional support, and intensive care handling are essential. With regard to local management, wounds should be treated with care, similar to the sterile procedures performed for severe thermal burns, to prevent epidermal detachment. Oozing areas are covered by nonstick dressings and changed at appropriate times based on local conditions. Antibiotics are utilized locally according to clinical sign of wound infection or wound cultures.

Role of systemic corticosteroids in the treatment of SJS/TEN is controversial. Engelhardt[16] claimed that corticosteroids given 48 hours or more prior to admission are associated with an increase in the incidence of infection, length of stay, and mortality. Kelemen et al.[17] indicated that steroid therapy was an independent factor for increased mortality in multivariate analysis of prognostic factors. Murphy[18] reported excessive mortality associated with prolonged use of systemic steroid therapy from retrospective review of 44 cases. Other opponents suggested an increased risk of sepsis, prolonged length of hospital stay, and increased mortality in TEN patients treated with corticosteroids[19, 20].However, several authors have concluded that the negative outcome of corticosteroids may related to the onset, dosage and length of therapy. Corticosteroids may indeed impair wound healing and promote sepsis.[21] Support for the use of corticosteroids has recently come from the publication of a large retrospective study[9]. They evaluated the effect on death of treatment administered after hospital admission in a cohort of 281 patients with SJS or TEN from France and Germany enrolled in EuroSCAR, a prospective case-control study of risk factors. The study displayed corticosteroids were more commonly used in Germany (87% of patients) than in France (45%), also with a higher maximum dose in Germany. Analyzing only patients with single-drug treatment, the authors observed a significant odds ratio for corticosteroids vs supportive care in Germany, but this was not validated by the outcomes in France. The authors suggested that their results were partly explained by the considerably higher dosage of corticosteroids use in Germany. Other study which supported the positive effect of systemic corticosteroids underscored the early initiation of treatment and high dosage[22, 23]. Kardaun et al[3] showed dexamethasone pulse therapy, 1.5 mg/kg/day, intravenously for three consecutive day reduced mortality rate predicted by SCORTEN. Tripathi et al.[24] demonstrated prompt treatment with corticosteroids in SJS may reduce morbidity. Our study supported the benefit of early treatment with systemic corticosteroids on survival. Also, no significant prolongation of hospital stay. Many reviewed mechanism of steroids in inhibiting inflamation has recently be proposed.[6,25,26]

Our study had limitations, according to retrospective nature of the study, we could not completely collect some important data, such as the SCORTEN and day of skin re-epithelization. For the rate of infection, it was difficult to determine whether some infection may be secondary to systemic corticosteroids.

Conclusions

1.The 3 most common drugs causing severe cutaneous adverse reaction (SCAR) in Ramathibodi Hospital during 2002-2009 were carbamazepine, trimethoprim-sulfamethoxazole and allopurinol.

2.From our study, systemic corticosteroids demonstrated potential benefit on survival and no evidence of prolonged hospitalization.

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References

1. Bastuji-Garin S, Rzany B, Stern RS, Shear NH, Naldi L, Roujeau JC. Clinical classification of cases of toxic epidermal necrolysis, Stevens-Johnson syndrome, and erythema multiforme. Arch Dermatol 1993;129:92-6.
2. 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;128:35-44.
3. Kardaun SH , Jonkman MF. Dexamethasone pulse therapy for Stevens-Johnson syndrome/toxic epidermal necrolysis. Acta Derm Venereol 2007;87:144-8.
4. Pereira FA, Mudgil AV, Rosmarin DM. Toxic epidermal necrolysis. J Am Acad Dermatol 2007; 56: 181-200.
5. Harr T, French LE. Toxic epidermal necrolysis and Stevens-Johnson syndrome. Orphanet J Rare Dis 2010;5:39.
6. Chave TA, Mortimer NJ, Sladden MJ, Hall AP, Hutchinson PE. Toxic epidermal necrolysis: current evidence, practical management and future directions. Br J Dermatol 2005;153:241-53.
7. Knowles S, Shear NH. Clinical risk management of Stevens-Johnson syndrome/toxic epidermal necrolysis spectrum. Dermatol Ther 2009;22:441-51.
8. Leenutaphong V, Sivayathorn A, Suthipinittharm P, Sunthonpalin P. Stevens-Johnson syndrome and toxic epidermal necrolysis in Thailand. Int J Dermatol 1993;32:428-31.
9. Schneck J, Fagot JP, Sekula P, Sassolas B, Roujeau JC , Mockenhaupt M. Effects of treatments on the mortality of Stevens-Johnson syndrome and toxic epidermal necrolysis: A retrospective study on patients included in the prospective EuroSCAR Study. J Am Acad Dermatol 2008;58:33-40.
10. Tassaneeyakul W, Tiamkao S, Jantararoungtong T, Chen P, Lin SY, Chen WH et al. Association between HLA-B*1502 and carbamazepine-induced severe cutaneous adverse drug reactions in a Thai population. Epilepsia 2010;51:926-30.
11. Kaniwa N, Saito Y, Aihara M, Matsunaga K, Tohkin M, Kurose K et al. HLA-B locus in Japanese patients with anti-epileptics and allopurinol-related Stevens-Johnson syndrome and toxic epidermal necrolysis. Pharmacogenomics 2008;9:1617-22.
12. Alfirevic A, Jorgensen AL, Williamson PR, Chadwick DW, Park BK , Pirmohamed M. HLA-B locus in Caucasian patients with carbamazepine hypersensitivity. Pharmacogenomics 2006;7:813-8.
13. Ferrell PB, Jr. , McLeod HL. Carbamazepine, HLA-B*1502 and risk of Stevens-Johnson syndrome and toxic epidermal necrolysis: US FDA recommendations. Pharmacogenomics 2008;9:1543-6.
14. Lonjou C, Borot N, Sekula P, Ledger N, Thomas L, Halevy S et al. A European study of HLA-B in Stevens-Johnson syndrome and toxic epidermal necrolysis related to five high-risk drugs. Pharmacogenet Genomics 2008;18:99-107.
15. Wolkenstein P , Revuz J. Toxic epidermal necrolysis. Dermatol Clin 2000;18:485-95, ix.
16. Engelhardt SL, Schurr MJ , Helgerson RB. Toxic epidermal necrolysis: an analysis of referral patterns and steroid usage. J Burn Care Rehabil 1997;18:520-4.
17. Kelemen JJ, 3rd, Cioffi WG, McManus WF, Mason AD, Jr. , Pruitt BA, Jr. Burn center care for patients with toxic epidermal necrolysis. J Am Coll Surg 1995;180:273-8.
18. Murphy JT, Purdue GF , Hunt JL. Toxic epidermal necrolysis. J Burn Care Rehabil 1997;18:417-20.
19. Halebian PH, Corder VJ, Madden MR, Finklestein JL , Shires GT. Improved burn center survival of patients with toxic epidermal necrolysis managed without corticosteroids. Ann Surg 1986;204:503-12.
20. Herndon DN. Toxic epidermal necrolysis: a systemic and dermatologic disorder best treated with standard treatment protocols in burn intensive care units without the prolonged use of corticosteroids. J Am Coll Surg 1995;180:340-2.
21. Wolf R , Davidovici B. Severe cutaneous adverse drug reactions: who should treat, where and how?: Facts and controversies. Clin Dermatol 2010;28:344-8.
22. van der Meer JB, Schuttelaar ML, Toth GG, Kardaun SH, Beerthuizen G, de Jong MC et al. Successful dexamethasone pulse therapy in a toxic epidermal necrolysis (TEN) patient featuring recurrent TEN to oxazepam. Clin Exp Dermatol 2001;26:654-6.
23. Stables GI , Lever RS. Toxic epidermal necrolysis and systemic corticosteroids. Br J Dermatol 1993;128:357.

24. Tripathi A, Ditto AM, Grammer LC, Greenberger PA, McGrath KG, Zeiss CR et al. corticosteroids therapy in an additional 13 cases of Stevens-Johnson syndrome: a total series of 67 cases. Allergy Asthma Proc 2000;21:101-5.
25. Paliogianni F, Raptis A, Ahuja SS, Najjar SM , Boumpas DT. Negative transcriptional regulation of human interleukin 2 (IL-2) gene by glucocorticoids through interference with nuclear transcription factors AP-1 and NF-AT. J Clin Invest 1993;91:1481-9.
26. Almawi WY , Melemedjian OK. Negative regulation of nuclear factor-kappaB activation and function by glucocorticoids. J Mol Endocrinol 2002;28:69-78.