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Prevalence and mortality rate of severe cutaneous adverse reactions at Siriraj Hospital

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Introduction : *Stevens-Johnson syndrome (SJS), Toxic Epidermal Necrolysis (TEN) and drug hypersensitivity syndrome (HSS) are severe cutaneous adverse reactions (SCAR) that is mostly related to drugs. Although incidence is rare, it has significant impact on patient's well being because of its high mortality rates.*

Objective : *To investigate the causative drugs, prevalence and mortality rates related to SCAR, which were from drug exposure during 2003 - 2007.*

Setting : *Siriraj Hospital, Bangkok.*

Research design : *A retrospective study*

Patients : *Patients who were diagnosed to be SJS, TEN and HSS were included.*

Method : *Five years retrospective data, 2003 - 2007, was collected from electronic database of Adverse Drug Reaction Monitoring Center and Siriraj Computer Center.*

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Result : *SCAR was found in 136 patients during 2003-2007 including 84 cases with SJS (61.76%), 3 cases with SJS overlap TEN (2.21%), 10 cases with TEN (7.35%) and 39 cases with HSS (28.68%). The prevalence of SJS, TEN and HSS were most often found in patients treated with carbamazepine, allopurinol and phenytoin, respectively. Mortality rate of SJS, TEN and HSS were 6.90%, 50.0% and 12.82% respectively.*

Conclusion : *Top three main drug groups causing SCAR were, namely: anti-convulsants (34.56%), antimicrobial (25.74%) and antigout (14.70%). Allopurinol revealed the highest mortality rate.*

Keywords : *Prevalence, Severe Cutaneous Adverse Reactions, Stevens-Johnson syndrome, toxic epidermal necrolysis, drug hypersensitivity syndrome.*

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ศุณิชา ลิ้มกอปรไพบูลย์, ดวงจิตต์ พนมวัน ณ อยุธยา, นฤมล ธนะ, โกวิทย์ จงเจริญประเสริฐ. ความชุกและอัตราการเสียชีวิตจากการเกิดอาการไม่พึงประสงค์ทางผิวหนังชนิดรุนแรงในโรงพยาบาลศิริราช. จุฬาลงกรณ์เวชสาร 2553 ก.ย. – ต.ค.; 54(5): 467 – 77

บทนำ : *Stevens-Johnson syndrome (SJS), Toxic Epidermal Necrolysis (TEN) และ Drug Hypersensitivity syndrome (HSS) เป็นอาการไม่พึงประสงค์ทางผิวหนังชนิดรุนแรง ซึ่งส่วนมากเกิดจากยาแม้ว่าอุบัติการณ์การเกิดค่อนข้างน้อย แต่ส่งผลกระทบที่รุนแรงทำให้ผู้ป่วยเสียชีวิตได้*

วัตถุประสงค์ : *เพื่อศึกษายาที่เป็นสาเหตุ ความชุกและอัตราการเสียชีวิตจากการเกิดอาการไม่พึงประสงค์ทางผิวหนังชนิดรุนแรงในโรงพยาบาลศิริราช.*

สถานที่ที่ทำการศึกษา : *โรงพยาบาลศิริราช*

รูปแบบการวิจัย : *การศึกษาย้อนหลัง*

ผู้ป่วยที่ได้ทำการศึกษา : *ผู้ป่วยที่ได้รับการวินิจฉัยจากแพทย์ว่าเป็น Stevens - Johnson syndrome, Toxic Epidermal Necrolysis และ Drug Hypersensitivity syndrome*

วิธีการศึกษา : *ผู้วิจัยรวบรวมรายชื่อยาที่เป็นสาเหตุจากศูนย์ติดตามอาการไม่พึงประสงค์จากการใช้ยาโรงพยาบาลศิริราชและรวบรวมจำนวนผู้ป่วยที่ได้รับยากลุ่มเสี่ยงในระหว่างปี 2546-2550 จากศูนย์คอมพิวเตอร์โรงพยาบาลศิริราช*

ผลการศึกษา : *พบอาการไม่พึงประสงค์ทางผิวหนังชนิดรุนแรงในผู้ป่วยทั้งหมด 136 ราย โดยแบ่งเป็น SJS 84 ราย (61.76%), SJS –TEN 3 ราย (2.21%), TEN 10 ราย (7.35%) และ HSS 39 ราย (28.68%) ความชุกของการเกิด SJS, TEN และHSS พบได้บ่อยในผู้ป่วยที่ได้รับการรักษาด้วยยา carbamazepine, allopurinol และ phenytoin ตามลำดับ อัตราการเสียชีวิตจาก SJS, TEN และ HSS เป็น 6.90%, 50.0% และ 12.82% ตามลำดับ*

วิจารณ์และสรุป : *กลุ่มยาที่เป็นปัญหาสำคัญ 3 อันดับแรกได้แก่ ยากันชัก (34.56%) ยาปฏิชีวนะ (25.74%) และยาต้านเกาต์ (14.70%) โดยพบว่า allopurinol เป็นยาที่เป็นสาเหตุให้ผู้ป่วยเสียชีวิตมากที่สุด*

คำสำคัญ : *ความชุก, Stevens-Johnson syndrome, Severe Cutaneous Adverse Reactions, Toxic Epidermal Necrolysis, Drug Hypersensitivity syndrome.*

More than 7% of people have experienced drug hypersensitivity that has significant impact to their lives.[1] Although the incidence of severe cutaneous adverse reactions (SCAR) including Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN) and drug hypersensitivity syndrome (HSS) that are delayed type immune-mediated reaction[2] are rare but they have significant impacts on patient's well being because of high mortality and morbidity rates. SJS and TEN are characterized by high fever, wide-spread blistering exanthema of macules and atypical target-like lesions, mucosal involvement is also found. SJS will be considered if less than 10% of the body surface area (BSA) of skin is detached. But if 10-30% of BSA of skin is detached, SJS overlap TEN is likely. While TEN is characterized by more than 30% of BSA detached.[3] Drug rash with eosinophilia and systemic symptoms (DRESS) or drug hypersensitivity syndrome is characterized by triad symptoms which include high fever, skin eruption (SJS/TEN, diffuse maculopapular rash, erythema multiforme or exfoliative dermatitis) and single or multiple internal organ involvement (especially acute hepatocellular injury, worsening renal function or hematological abnormalities).[4, 5] More than 70% of the cases were drug-induced.[6, 7] Few studies on SCAR and there are no reported studies in drug hypersensitivity syndrome in Thailand which might due to its rarity and clinical heterogeneity of HSS makes diagnosis difficult. Hence, the purposes of this study were to investigate the causative drugs, the prevalence and mortality rates related to SCAR, which were from drug exposure during 2003 - 2007 of patients at Siriraj Hospital.

Methods

A retrospective study design was used. The protocol was approved by Siriraj Institutional Review Board (SIRB), Siriraj Hospital, Mahidol University. Five years retrospective data, during 2003 - 2007, were reviewed using electronic database of Adverse Drug Reaction Monitoring Center, Siriraj Hospital. Both inpatients and outpatients who were diagnosed by dermatologists to be SJS, TEN and HSS were included. The following data were collected from electronic database: 1) demographic data; 2) causative drugs; 3) prevalence of SJS, TEN and HSS; 4) onset time of symptom after causative drug had been administered; 5) duration of hospitalization; and, 6) clinical outcomes. Prevalence of SCAR was calculated using the number of patients who experienced SCAR compared to the total number of patients who received the drugs during 5 years (the later data were collected from Siriraj Computer Center, Siriraj Hospital.) Data collected were complied on Microsoft Excel sheet and subjected to descriptive statistical analysis.

Results

Demographic data

SCAR was found in 136 patients. Most patients were hospitalized, (81.62%). The proportion of female and male was not different (1.2:1). The mean age was 46.68 $\pm$ 20.50 years old (range 4 months – 88 years). It was the fact that adults experienced more frequently adverse drug reaction rather than children. SCAR in adults was not different among age group. The data are summarized in Table 1, ;84 cases with SJS (61.76%); 3 cases with SJS overlap TEN (2.21%); 10 cases with TEN (7.35%) and 39 cases with HSS (28.68%).

Table 1. Demographic data of patients with SCAR (n=136)

Demographic data	SJS*N(%)	TEN N(%)	HSS N(%)	SCAR N(%)
Number of patients	87(63.97)	10 (7.35)	39 (28.68)	136 (100)
Type of patients				
Outpatient	23 (26.44)	0 (0)	2 (5.13)	25 (18.38)
Inpatient	64 (73.56)	10 (100)	37 (94.87)	111 (81.62)
Gender				
Female	51 (58.62)	5 (50.0)	18 (46.15)	74 (54.41)
Male	36 (41.38)	5 (50.0)	21 (53.85)	62 (45.59)
Age (years, mean ± SD)	(48.21 ± 18.43)	(51.10 ± 18.80)	(42.13 ± 24.69)	(46.68 ± 20.51)
median	46	41	44	45
0-12	1 (1.15)	0 (0)	5 (12.82)	6 (4.41)
13- 20	4 (4.60)	0(0)	4(10.26)	8 (5.88)
21-40	27 (31.03)	5 (50.0)	8 (20.51)	40 (29.41)
41-60	28 (32.18)	1 (10.0)	12 (30.76)	41 (30.14)
over 60	27 (31.03)	4 (40.0)	10 (25.64)	41 (30.14)
Number of dead	6 (6.90%)	5 (50.0%)	5 (12.82%)	16 (11.76%)

*SJS and SJS overlap TEN

Drugs with high prevalence as the cause of SCAR

SCAR was found most frequently in the anticonvulsant drug group (34.56%); the second and the third were the antimicrobial (25.74%) and anti-gout (14.70%), respectively. Drug groups frequently found to be the cause of SCAR are shown in Table 2. The top five drugs most frequently reported to be the cause of SCAR were, namely: phenytoin, allopurinol, cotrimoxazole, carbamazepine and, nevirapine and phenobarbital. The highest prevalence of SJS, TEN and HSS were found with carbamazepine, allopurinol and phenytoin which the rates were 3.26, 0.21 and 2.64 per 1000 patients, respectively, as shown in Table 3.

Onset of symptoms, duration of hospitalization and Mortality rate

Mean onset time of SCAR after the administration of causative drug was 20.12 ± 15.98 (median, 16) days (range 1 to 98 days). Mean onset times of SJS, SJS overlap TEN, TEN and HSS, were 18.29 ± 13.38 (median, 15) days, 12 ± 8.54 (median, 13) days, 13.50 ± 10.85 (median, 12) days and 26.24 ± 20.39 (median, 23) days respectively. Mean duration of hospitalization was 20.69 ± 22.72 (median, 13) days. Mean duration of hospitalization when categorized by event; SJS, SJS overlap TEN, TEN and HSS, were 18.13 ± 14.58 days (median, 12), 21.00 ± 19.16 days (median, 12), 22.50 ± 11.77 days (median, 23) and 24.60 ± 34.32 (median, 13) days respectively. HSS showed longer period of hospitalization (range 4 to 185 days). Mortality rate of SJS, TEN and HSS were 6.90%, 50.0% and 12.82% respectively. Twenty- five percent of all death cases were related to allopurinol, the highest mortality generator, the details are in Table 4.

Table 2. Drugs of causing SCAR.

Causative drug	SJS*	TEN	HSS	Total
Anticonvulsant	21	1	25	47 (34.56)
Carbamazepine	9(1*)	0	1	11 (8.09)
Phenytoin	9	1	19	29 (21.32)
Phenobarbital	1	0	5	6 (4.41)
Sodium valproate	1	0	0	1 (0.74)
Antimicrobial	29	4	2	35 (25.74)
Sulfonamide	14(1*)	0	2	17 (12.50)
Penicillin	4	0	0	4 (2.94)
Cephalosporin	2	1	0	3 (2.20)
Carbapenem	1	1	0	2 (1.47)
Quinolone	5	1	0	6 (4.41)
Glycopeptides	1	0	0	1 (0.74)
Lincosamide	0	1	0	1 (0.74)
Misc.(dapsone)	1	0	0	1 (0.74)
Allopurinol	13	2	5	20 (14.70)
Antiviral	5	0	1	6 (4.41)
Nevirapine	5	0	1	6 (4.41)
NSAIDs	3	0	1	4 (2.94)
Dipyrone	1	0	0	1 (0.74)
Ibuprofen	1	0	1	2 (1.47)
Mefenamic acid	1*	0	0	1 (0.74)
Total of five groups	71	7	34	112 (82.35)
Others	16	3	5	24 (17.65)
Total	87	10	39	136 (100)

*include SJS overlap TEN

Table 3. Top five high risk drugs with prevalence of SCAR.

Causative drug	SJS	TEN	HSS	SCAR
Phenytoin	1.25	0.14	2.64	4.03
Carbamazepine	3.26	0	0.33	3.59
Nevirapine	2.79	0	0.56	3.35
Cotrimoxazole	2.77	0	0.37	3.14
Allopurinol	1.39	0.21	0.53	2.13
Phenobarbital	0.29	0	1.44	1.73

Prevalence 1:1000 patients using the causative drug in 5 years

Table 4. Mortality and the causative drug.

Age/Sex	Causative drug	Reaction	Complications	Cause of death
79/F	Allopurinol	SJS	Metabolic acidosis	Septic shock
83/F	Allopurinol	SJS	Septicemia	Pneumonia with septic shock
78/M	Allopurinol	SJS	Respiratory failure ARF	VAP with septic shock
42/M	Allopurinol	TEN	ARSD, ARF, VAP, DIC, Septicemia	Septic shock
31/M	Isoniazid	TEN	Acute hepatitis	fulminant hepatic failure
24/F	Isoniazid	HSS	Hepatic encephalopathy, DIC, Hypernatremia, GI bleeding	fulminant hepatic failure
77/F	Carbamazepine	SJS	ARF, Metabolic acidosis, Hyperphosphatemia, UTI	Septic shock
69/F	Cefotaxime	SJS	Pulmonary collapse, Plural effusion, Septicemia	Septicemia
75/F	Clindamycin	TEN	ARF, pneumonia, Hepatic failure, DIC, GI bleeding	Septic shock
51/M	Dipyrone[$]	HSS	Septicemia	Multiple organ failure
65/F	Ibuprofen	HSS	Respiratory failure, DVT, severe pneumonia	Respiratory failure, Septic shock
76/F	Imipenam+cilastatin	TEN	Pneumonia	Septic shock
1/M	Phenobarbital	HSS	Pulmonary edema, DIC Electrolyte imbalance	DIC, septic shock
79/F	Phenytoin	HSS	HAP, Acute pyelonephritis	HAP
40/F	Propylthiouracil	TEN	DIC, pneumonia, Acute diarrhea	Septic shock
29/M	Vancomycin	SJS	Meningitis	Brain hemiation hydrocephalus

[$] Secondary exposure; VAP,Ventilator-associated pneumonia; ARF, Acute renal failure; ARSD, Acute respiratory distress syndrome; DIC, Disseminated intravascular coagulation; HAP, Hospital acquired pneumonia; DVT, Deep vein thrombosis; UTI, Urinary tract infection

Discussion

When categorized by group of causative drugs, anticonvulsants shared one- third of all reported cases of SCAR. Consistent results were reported from India, Malaysia and Srinagarind Hospital. [6, 8, 9] In this study, phenytoin, carbamazepine and phenobarbital were the main causative drugs. These three drugs have similarity in their chemical structures; they all are aromatic anticonvulsants which are metabolized in the liver by cytochrome P450 enzyme. The arene oxide metabolites which are the product of this metabolic pathway can cause cellular toxicity by activating self-destruction of the immune system. [10] Phenytoin had the highest prevalence of HSS; the rate was approximately 2-3 per 1000 patients. Approximately, 3-4 per 1000 patients using carbamazepine who experienced SJS were from carbamazepine usage. This drug can activate SJS/TEN by binding Major Histocompatibility Complex (MHC) and the T cell receptor.[9] In this study, over 80% of adverse drug reactions from phenobarbital were found in children due to the more frequently usage of this drug in children than in adults. Special precaution of cross-reaction has to be concerned if patients experience severe adverse drug reaction with these drugs, 45 - 75% of cross–reaction had been reported. [11, 12] Recently, there were few studies that showed strong association between human leukocyte antigen allele B*1502 (HLA-B*1502 allele) and carbamazepine induced SJS/TEN in the Han Chinese, Thai and Indian patients. [13, 14, 15] The United States Food and Drug Administration (USFDA) recommend genetic screening of this allele for all carbamazepine users in Asians[16] since high frequency of this allele has been reported in Asian population.[1]

The other drug group frequently found to be the cause of SCAR was antimicrobial (25.73%). Sulfonamides was found to be the highest cause of SJS and HSS while previous similar study at Siriraj Hospital in 1993 revealed that penicillin was the main cause of SJS/TEN during that period.[7] This should be due to the increasing usage of cotrimoxazole for opportunistic infection prophylaxis in human immunodeficiency virus (HIV) patients. HIV patients have higher probability of confronting with adverse drug reaction from cotrimoxazole, approximately 18 - 57%, as compared to the adverse drug reaction rate of 3% in overall patients. Glutathione deficiency, co-infection of the cytomegalovirus or Epstein-Barr virus in HIV patients might be the reason of this circumstance.[17] SJS/TEN were also found in quinolone drugs usage but with fewer incidences than in the sulfonamides usage group. Moreover, allopurinol is the only one drug that all symptoms, SJS/TEN and HSS, have been reported. If HSS only was considered, allopurinol became the most often reported HSS causative drug. Pathogenesis of allopurinol hypersensitivity syndrome is unclear; its etiology is related to many factors including immunology, genetics, and accumulation of oxypurinol and reactivate of latent virus. [18] One out of five patients who experienced SCAR from allopurinol died. There were studies that clearly showed the association between HLA-B*5801 allele and allopurinol induced SJS and TEN in the Han Chinese and Thai patients. [19,20] Non-steroidal anti-inflammatory (NSAIDs) was found less often as SCAR causative than the first three drug groups while higher mortality rate was observed. Oxicam one group of the NSAIDs which had been reported to be high-risk

drugs in other study[21] did not appear in our high-risk drug list.

Comparisons of the mean onset times of SCAR after causative drug administration revealed that HSS had longer incubation time as compared to SJS and TEN. However, mortality rate in this study was quite similar to previous studies which reported the mortality rate of SJS TEN and HSS to be 5%[22], 30-50%[22] and 8-20% [23 - 25] respectively. The overall mortality rate in this study was 11.76%. This high mortality rate indicated that severity of the event has not been decreased from the past despite evolutionary of medical care. Probably Siriraj Hospital is the tertiary care setting and 25% of the death cases with very severe clinical symptom were referred from other health- care settings, hence, overall mortality rate was higher than those previously reported from other settings. *N*-acetylcysteine (NAC) is used for the treatment of SJS and TEN, more often than intravenous immunoglobulin (IVIG), since NAC is less expensive and assumed to act as an antioxidant, help generating glutathione and inhibit production of tumor necrosis factor α (TNF- α) and interleukin-1 (IL-1).[26]

Conclusion

This study reveals that, the three main SCAR causative drug groups found at Siriraj Hospital were anticonvulsant, antimicrobial and anti-gout. The events had significant impacts on patients, for example death or disability. Drugs with top prevalence of SCAR were phenytoin, carbamazepine, nevirapine, cotrimoxazole, allopurinol and phenobarbital. Mortality rates of SJS, TEN and HSS were 6.90%, 50.0% and 12.82%, respectively. Allopurinol was associated with the highest mortality rate.

In the future, genetic screening may be a benefit for good clinical practice in order to prevent severe adverse drug reactions from the usage of all these high risk drugs.

References

1. Chung WH, Hung SI, Chen YT. Human leukocyte antigens and drug hypersensitivity. Curr Opin Allergy Clin Immunol 2007 Aug;7(4):317-23
2. Lonjou C, Borot N, Sekula P, Ledger N, Thomas L, Halevy S, Naldi L, Bouwes-Bavinck JN, Sidoroff A, de Toma C, 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 Feb;18(2):99-107
3. French LE. Toxic epidermal necrolysis and Stevens Johnson syndrome: our current understanding. Allergol Int 2006 Mar;55(1): 9-16
4. ฐิติมา ด้วงเงิน. ภาคผนวก (DRESS syndrome). ใน: ธิดา นิงสานนท์, จันทิมา โยธาพิทักษ์. ตรงประเด็นเรื่อง Adverse Drug Reaction. กรุงเทพ: ปรมัตถ์ การพิมพ์, 2549: 147-9.
5. Markel A. Allopurinol-induced DRESS syndrome. Isr Med Assoc J 2005 Oct;7(10):656-60
6. Jantararoungtong T, Tiamkao S, Vanaprasath S, Choonhakarn C, Auvichayapat N, Tassaneeyakul W. Stevens-Johnson syndrome and toxic epidermal necrolysis in Srinagarind Hospital: a retrospective study of causative drugs and clinical outcome. Thai J Pharmacol 2009;31(1):41-4
7. Leenutaphong V, Sivayathorn A, Suthipinittharm P, Sunthonpalin P. Stevens-Johnson syndrome

and toxic epidermal necrolysis in Thailand. Int J Dermatol 1993 Jun;32(6):428-31

8. Sharma V, Sethuraman G, Minz A. Stevens Johnson syndrome, toxic epidermal necrolysis and SJS-TEN overlap: a retrospective study of causative drugs and clinical outcome. Indian J Dermatol Venereol Leprol 2008 May-Jun;74(3):238-40
9. Yap F, Wahiduzzaman M, Pubalan M. Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) in Sarawak: a four years' review. Egyptian Dermatology Online JI 2008 Jun;4(1):1-13
10. Shear NH, Spielberg SP. Anticonvulsant hypersensitivity syndrome. In vitro assessment of risk. J Clin Invest 1988 Dec; 82(6):1826-32
11. Mansur AT, Pekcan YS, Goktay F. Anticonvulsant hypersensitivity syndrome: clinical and laboratory features. Int J Dermatol 2008 Nov; 47(11):1184-9
12. Sierra NM, Garcia B, Marco J, Plaza S, Hidalgo F, Bermejo T. Cross Hypersensitivity Syndrome between Phenytoin and Carbamazepine. Pharm World Sci 2005 Jun;27(3):170-4
13. Man CB, Kwan P, Baum L, Yu E, Lau KM, Cheng AS, Ng MH. Association between HLA-B*1502 allele and antiepileptic drug-induced cutaneous reactions in Han Chinese. Epilepsia 2007 May;48(5):1015-8
14. Locharernkul C, Loplumlert J, Limotai C, Korkij W, Desudchit T, Tongkobpetch S, Kangwanshiratada O, Hirankarn N, Suphapeetiporn K, Shotelersuk V. Carbamazepine and phenytoin induced Stevens-Johnson syndrome is associated with HLA-B*1502 allele in Thai population. Epilepsia 2008 Dec;49(12):2087-91
15. Mehta TY, Prajapati LM, Mittal B, Joshi CG, Sheth JJ, Patel DB, Dave DM, Goyal RK. Association of HLA-B*1502 allele and carbamazepine-induced Stevens-Johnson syndrome among Indians. Indian J Dermatol Venereol Leprol 2009 Nov;75(6):579-82
16. Ferrell PB Jr, McLeod HL. Carbamazepine, HLA-B*1502 and risk of Stevens-Johnson syndrome and toxic epidermal necrolysis: US FDA recommendations. Pharmacogenomics 2008 Oct;9(10):1543-6
17. ปวีณา สนธิสมบัติ. Currrent issues of penicillin and sulfa drugs allergy and management. ใน : บุษบา จินดาวิจักษ์, สุวัฒทนา จุฬาวัฒนทล, เนติ สุขสมบูรณ์, วิมล อนันตสกุลวัฒน์, สุรกิจ นาทีสุวรรณ, ปรีชา มนทกานติกุล. การบริบาลทางเภสัชกรรมเพื่อความปลอดภัยของผู้ป่วย. กรุงเทพ: สำนักพิมพ์ประชาชน, 2547: 198.
18. Lee HY, Ariyasinghe JT, Thirumoorthy T. Allopurinol hypersensitivity syndrome: a preventable severe cutaneous adverse reaction? Singapore Med J 2008 May;49(5): 384-7
19. Hung SI, Chung WH, Liou LB, Chu CC, Lin M, Huang HP, Lin YL, Lan JL, Yang LC, Hong HS, et al. HLA-B*5801 allele as a genetic marker for severe cutaneous adverse reactions caused by allopurinol. Proc Natl Acad Sci U S A 2005 Mar;102(11):4134-9
20. Tassaneeyakul W, Jantararoungtong T, Chen P, Lin PY, Tiamkao S, Khunarkornsiri U, Chucherd P, Konyoung P, Vannaprasaht S,

Choonhakarn C, et al. Strong association between HLA-B*5801 and allopurinol-induced Stevens-Johnson syndrome and toxic epidermal necrolysis in a Thai population. Pharmacogenet Genomics 2009 Sep;19(9):704-9

21. Roujeau JC, Kelly JP, Naldi L, Rzany B, Stern RS, Anderson T, Auquier A, Bastuji-Garin S, Correia O, Locati F, et al. Medication use and the risk of Stevens-Johnson syndrome or toxic epidermal necrolysis. N Engl J Med 1995 Dec;333(24):1600-7
22. Chia FL, Leong KP. Severe cutaneous adverse reactions to drugs. Curr Opin Allergy Clin Immunol 2007 Aug;7(4):304-9
23. Seth D, Kamat D, Montejo J. DRESS syndrome: a practical approach for primary care practitioners. Clin Pediatr (Phila) 2008 Nov; 47(9):947-52
24. Eshki M, Allanore L, Musette P, Milpied B, Grange A, Guillaume JC, Chosidow O, Guillot I, Paradis V, Joly P, et al. Twelve-year analysis of severe cases of drug reaction with eosinophilia and systemic symptoms: a cause of unpredictable multiorgan failure. Arch Dermatol 2009 Jan;145(1):67-72
25. Shiohara T, Inaoka M, Kano Y. Drug-induced hypersensitivity syndrome (DIHS): a reaction induced by a complex interplay among herpesviruses and antiviral and antidrug immune responses. Allergol Int 2006 Mar; 55(1):1-8
26. Velez A, Moreno JC. Toxic epidermal necrolysis treated with N-acetylcysteine. J Am Acad Dermatol 2002 Mar;46(3):469-70