นิพนธ์ต้นฉบับ . Original Article

ระบาดวิทยาของอาการไม่พึงประสงค์ทางผิวหนังชนิดรุนแรงจากการใช้ยาในโรงพยาบาลระดับภูมิภาคตะวันออกเฉียงเหนือของประเทศไทย

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Epidemiology of Severe Cutaneous Adverse Drug Reactions in a Northeastern Region of Thailand

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Received: 22 January 2025/ Review: 22 January 2025/ Revised: 27 March 2025/ Accepted: 28 March 2025

บทคัดย่อ

หลักการและวัตถุประสงค์: อาการไม่พึงประสงค์ทางผิวหนังชนิดรุนแรงจากยา (severe cutaneous adverse drug reactions, SCARs) จัดเป็นอาการไม่พึงประสงค์ที่มักไม่สัมพันธ์กับกลไกการออกฤทธิ์ของยา มีอัตราการเสียชีวิตสูงและมีผลกระทบต่อสุขภาพอย่างมีนัยสำคัญทางสถิติ ดังนั้นการศึกษานี้จึงมีวัตถุประสงค์เพื่อศึกษาถึงยาที่คาดว่าเป็นสาเหตุ ลักษณะทางคลินิก การรักษา และผลลัพธ์จากการแพ้ยาในผู้ป่วยแพ้ยาแบบ SCARs ที่เข้ารับการรักษาในโรงพยาบาลระดับภูมิภาคตะวันออกเฉียงเหนือของประเทศไทย

วิธีการศึกษา: รวบรวมและคัดเลือกผู้ป่วยแพ้ยาแบบ SCARs ที่รับการรักษาในโรงพยาบาลขอนแก่น ช่วงปี พ.ศ. 2562-2566 โดยใช้ Naranjo algorithm สำหรับประเมินยาที่คาดว่าเป็นสาเหตุ และรวบรวมข้อมูลประชากรและข้อมูลทางคลินิกจากเวชระเบียนของผู้ป่วย

ผลการศึกษา: ผู้ป่วยแพ้ยาแบบ SCARs ที่เข้าร่วมโครงการวิจัย มีทั้งหมด 64 ราย แบ่งเป็นการแพ้ยาแบบ Steven-Johnson syndrome (SJS) มากที่สุด (28 ราย) รองลงมา คือการแพ้ยาแบบ drug reaction with eosinophilia and systemic symptoms (DRESS), toxic epidermal necrolysis (TEN), SJS/TEN overlap และ acute generalized exanthematous pustulosis (AGEP) ตามลำดับ อายุเฉลี่ยของผู้ป่วยเท่ากับ 50.50 ± 18.18 ปี เป็นเพศชายร้อยละ 51.46 ยาที่คาดว่าเป็นสาเหตุของ SCARs ที่พบมากที่สุด ได้แก่ กลุ่มยาต้านจุลชีพ (ร้อยละ 48.43) รองลงมา คือ กลุ่มยากันชัก (ร้อยละ 23.44) และ ยา allopurinol (ร้อยละ 18.75) ค่าเฉลี่ยของระยะเวลาตั้งแต่ได้รับยาจนกระทั่งเกิด SCARs เท่ากับ 23.59 ± 26.39 วัน ค่าเฉลี่ยระยะเวลาอยู่โรงพยาบาลเท่ากับ 10.19 ± 11.23 วัน โดยกลุ่มผู้ป่วย TEN มีระยะเวลาอยู่โรงพยาบาลและค่าใช้จ่ายในการรักษาสูงที่สุด ส่วนอัตราการเสียชีวิตจาก SCARs พบเพียง 1 รายที่เสียชีวิตขณะเกิด SCARs ซึ่งเป็นผู้ป่วยแพ้ยาแบบ TEN จากยา allopurinol สำหรับการรักษาพบว่าการใช้ยากลุ่ม immunomodulating agents ได้แก่ corticosteroids, cyclosporine A หรือ intravenous immunoglobulin (IVIg) มีประสิทธิภาพในการรักษา SCARs

สรุป: การศึกษานี้ให้ข้อมูลเชิงลึกเกี่ยวกับระบาดวิทยาของการแพ้ยาแบบ SCARs ซึ่งมีประโยชน์และช่วยพัฒนาแนวปฏิบัติทางคลินิก โดยข้อมูลดังกล่าวช่วยส่งเสริมความตระหนักรู้ การวินิจฉัยที่รวดเร็วและแม่นยำ การจัดการหรือการรักษาที่เหมาะสม รวมถึงการเพิ่มความปลอดภัยของผู้ป่วย

คำสำคัญ: อาการไม่พึงประสงค์ทางผิวหนังชนิดรุนแรงจากการใช้ยา, กลุ่มอาการสตีเวน-จอห์นสัน, ผิวหนังชั้นนอกที่เป็นพิษ, ปฏิกิริยาของยาที่ทำให้เกิดภาวะอีโอซิโนฟิลและอาการทั่วร่างกาย, ตุ่มหนองแบบผื่นแดงเฉียบพลันทั่วไป

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Abstract

Background and Objective: Severe cutaneous adverse reactions (SCARs) are generally unrelated to the mechanism of action of the drug and are associated with significant mortality as well as both short- and long-term morbidity. Epidemiological data on SCARs vary based on regional drug use patterns and health issues. This study aimed to investigate the causative drugs, clinical characteristics, treatment, and outcomes of SCARs in hospitalized patients diagnosed with drug-induced SCARs at a northeastern region of Thailand.

Methods: Patients admitted to Khon Kaen Hospital for SCARs or who developed SCARs during hospitalization for other conditions between 2019 and 2023 were recruited. Drug causality was assessed using the Naranjo algorithm. Demographic and clinical data were reviewed and collected from medical records.

Results: Among 64 patients diagnosed with SCARs, the most common phenotype were SJS (28 patients), followed by DRESS, TEN, SJS/TEN overlap, and AGEP. The average age of SCARs patients was 50.50 ± 18.18 years, with 51.46% being male. Antimicrobial agents (48.43%) were the most common causative drugs, followed by anticonvulsants (23.44%) and allopurinol (18.75%). The average onset of SCARs was 23.59 ± 26.39 days. The average length of hospital stay for SCARs treatment was 10.19 ± 11.23 days. TEN patients had the longest hospital stays and highest cost of treatment. Only one patient with TEN induced by allopurinol died at SCARs episode. Immunomodulating agents, including corticosteroids, cyclosporine A, or IVIg, were beneficial in treatment of SCARs.

Conclusions: This study provides valuable insights into the epidemiological data of SCARs, enhancing clinical practice by promoting awareness, earlier diagnosis, proper management and improved patient safety.

Keywords: severe cutaneous adverse drug reactions, Steven-Johnson syndrome, toxic epidermal necrolysis, drug reaction with eosinophilia and systemic symptoms, acute generalized exanthematous pustulosis

Introduction

Severe cutaneous adverse drug reactions (SCARs) are a group of adverse drug reactions resulting from T-cell mediated or delayed type IV drug hypersensitivity reactions which require a few days to weeks for disease onset after drug exposure[1]. These reactions are life-threatening reactions and consists of several forms of skin eruptions and systemic involvement including Stevens–Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), drug reaction with eosinophilia and systemic symptoms (DRESS) and acute generalized exanthematous pustulosis (AGEP)[1,2]. SJS and TEN are the most serious types of SCARs that the clinical manifestations of these reactions include a prodrome of fever and early mucosal involvement, followed by atypical target lesions, widespread blistering cutaneous eruptions, positive Nikolsky sign with epidermal detachment, extensive mucosal erosions especially eye, mouth, and genital[1,2]. SJS and TEN are considered as the same disease, common causes and mechanisms but different in the extent of skin detachment[1] in which SJS is defined as skin detachment of less than 10% of total body surface area (TBSA), TEN involves more than 30%, and SJS/TEN overlap between 10-30% of TBSA[1,3,4]. Moreover, the severity of SJS/TEN can be predicted from clinical manifestations by using a Severity-of-Illness Score for Toxic Epidermal Necrolysis (SCORTEN)[5]. In contrast with SJS/TEN, the clinical manifestations of DRESS present less mucosal involvement and skin detachment. DRESS is characterized by fever, extensive skin rash, facial edema, lymphadenopathy, hematological abnormalities especially eosinophilia and internal organ involvements[1,2]. AGEP is characterized by acute formation of sterile pustules on an erythematous background, fever and neutrophilia[6,7].

The mortality rates of SJS/TEN usually relate with the degree of skin detachment and vary between 5-20% and up to 50% in TEN. While the mortality rates of DRESS and AGEP are less than 10% and 5%, respectively[2,6,7]. Moreover, the patients who recover from SCARs episodes may be left with long-term sequelae or some complications such as visual impairment, skin sensitivity, hypo/hyperpigmentation in patients with SJS/TEN and autoimmune diseases in patients with DRESS[2,7].

The common causative drugs of SCARs reported in previous studies were antibiotics, anticonvulsants, uric acid lowering agents and non-steroidal anti-inflammatory drugs (NSAIDs)[2,8,9]. Early identification of the causative drugs not only allows prompt withdrawal of the causative drugs, but also improves the prognosis and outcomes of SCARs treatment. Nevertheless, studies in the Thai population have demonstrated variability in etiological factors and clinical presentations of drug-induced SCARs[9-11]. Additionally, there is limited information regarding optimal treatment strategies and associated outcomes within this population[9-11]. Given that epidemiological patterns of SCARs may vary due to regional differences in drug prescription practices and local health challenges, comprehensive data specific to Thailand, particularly at the regional level, are essential. Therefore, the present study aimed to explore the causative drugs, clinical characteristics, treatment, and outcomes of SCARs in hospitalized patients diagnosed with drug-induced SCARs in a regional hospital in Northeastern region of Thailand.

Patients and Methods

Study population

The patients who had been admitted to Khon Kaen Hospital for treatment of drug-induced SCARs or suffering from drug-induced SCARs during admission for treatment of other diseases between 2019 and 2023 were recruited to the study. All patients with drug-induced SCARs were diagnosed primarily by an internist or residents in the Department of Medicine and subsequently confirmed by a dermatologist based on the sign and symptom of the patient including the pattern of skin eruption, percentage of skin detachment, timeline relation between SCARs onset and drug exposure, and laboratory test. SJS and TEN were defined as

widespread developing blistering exanthema of purpuric macules and target-like lesions with skin detachment and mucosal involvement[5,6]. The disease severity of SJS/TEN based on predicted mortality rates was also evaluated by using a TEN-specific severity-of-illness score (SCORTEN)[5], which predicts mortality rates of 90.0% for scores ≥ 5, 58.3% for a score of 4, 35.3% for a score of 3, 12.1% for a score of 2, and 3.2% for scores between 0 and 1[5].The criteria for DRESS included cutaneous involvement with a typical rash, fever, eosinophilia or atypical lymphocytes, facial edema, lymphadenopathy and internal organ involvements and all DRESS cases were also evaluated by using scoring system (DRESS score) from RegiSCAR group[12-14]. AGEP was defined as fever, numerous small, mostly non-follicular, sterile pustules arise on a widespread erythematous base[15,16]. The study protocol was approved by the Ethics Committee for Human Research, Khon Kaen Hospital (KEXP66054) and Khon Kaen University (HE510837).

Drug causality assessment

Drugs that the patients received within 3 months before the onset of SCARs manifestations were evaluated as possible causative drugs based on the criteria of the Naranjo algorithm[17]. The causative drugs were assessed primarily by a pharmacist who was responsible for the adverse drug reaction surveillance activity in Khon Kaen Hospital and confirmed by a pharmacist in the investigator team. Only patients in whom drugs was identified with a probable to a very probable/definite cause of SCARs (Naranjo adverse drug reaction score of ≥5) were recruited in the study.

Data collection

Data were retrospectively collected from electronic medical records, including demographics, medical history (including indication and dates of initiation and discontinuation of drugs), medical comorbidities or underlying diseases, physical examination, laboratory data, timing of SCARs onset (defined as the onset of skin symptoms). Additionally, the outcomes associated drugs-induced SCARs were collected, including length of hospital admission for treatment of SCARs (counted from the first day that the patients had been diagnosed for SCARs to the day that the patient discharged from the hospital), cost of treatment, and mortality rates.

Data and statistical analysis

Descriptive statistics were used to examine the frequency and distribution of covariates of interest. Comparisons between groups were made using Chi-square analysis or Fisher's exact test for categorical variables and the one-way ANOVA test or the Kruskal-Wallis test for numerical variables. A P-value of less than 0.05 was considered statistically significant. All statistical analyses were performed using SPSS statistical software, version 25.0 for Windows (IBM, Armonk, New York, USA).

Results

Demographic data

Among 64 drug-induced SCARs patients were recruited in the study, SJS was the most common phenotype of SCARs (28 cases, 43.75%), followed by DRESS (25 cases, 39.06%), TEN (5 cases, 7.81%), SJS/TEN overlap (5 cases, 7.81%) and AGEP (1 case, 1.56%). The SCARs patients comprised of 33 men (51.46%) and 31 women (48.44%) with an average age of 50.50 ± 18.18 years (range from 17 to 84 years). The most common comorbidities in these patients included HIV infection (25%), hypertension (21.88%), diabetes mellitus (17.19%), gout (15.63%) and epilepsy (12.50%). All demographic and clinical data of the patients are shown in Table 1.

Causative drugs of SCARs

According to the therapeutic classification of drugs, seven drug classes were identified as causative drugs of SCARs in which the antimicrobial agents were the most common causative drug of SCARs (48.43%), followed by anticonvulsant drugs (23.44%) and urate

lowering agent (allopurinol) (18.75%). Other causative drug classes were antituberculosis drugs, antiviral agents, non-steroidal anti-inflammatory drugs (NSAIDs) and proton pump inhibitors (PPIs) (Figure 1).

Moreover, subgroup analysis for causative drugs based on SCARs phenotypes was presented in Table 2. The top five most common causative drugs for SJS and TEN were co-trimoxazole, allopurinol, phenytoin, carbamazepine and ceftriaxone. While the top five most common causative drugs for DRESS were allopurinol, followed by co-trimoxazole, phenytoin carbamazepine and amoxicillin/clavulanic acid. Only one AGEP case was enrolled into this study and the causative drug of this AGEP case was norfloxacin.

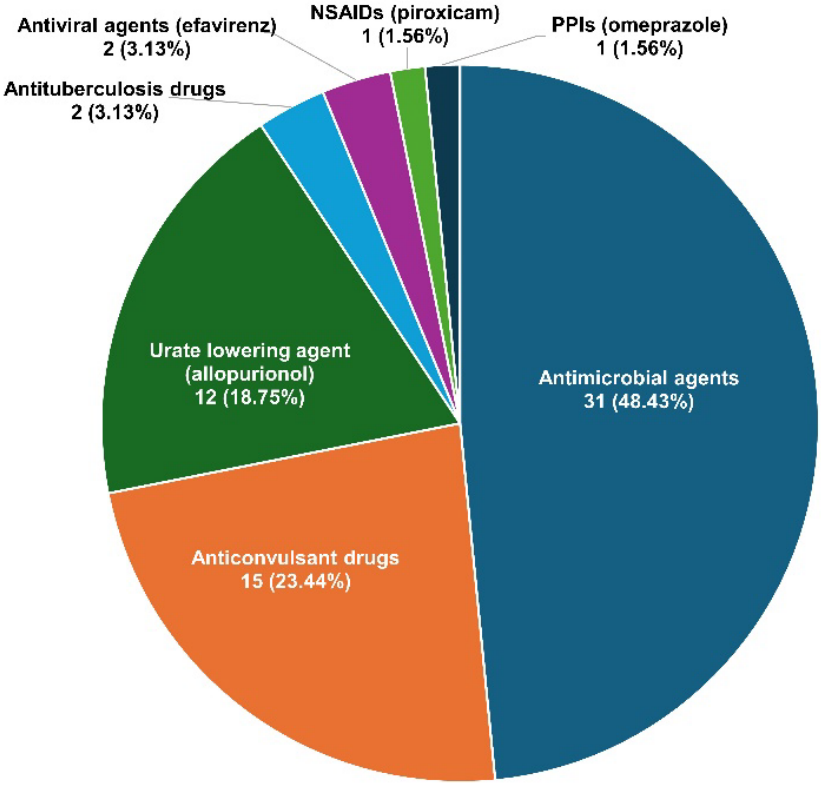

Figure 1 Causative drugs of SCARs

Clinical characteristics and outcomes of SCARs

Onset of SCARs

The intervals between drug initiation and the occurrence of first signs of SCARS (onset) were presented in Table 3. The average onset of SCARs was 23.59 ± 26.39 (range from 1-138) days. When focusing on the phenotypes of SCARs, it found that the onset was 20.43 ± 15.40 (range from 1-56) days in SJS, 11.60 ± 14.17 (range from 1-36) days in SJS/TEN overlap and 23 ± 14.11 (range from 10-42) days in TEN, whereas those of drugs-induced DRESS was 30.44 ± 26.39 (range from 1-138) days. For AGEP case, the onset of drug-induced AGEP was 4 days.

Mucosal involvements

Apart from skin lesion, mucosal involvements were presented during SCARs episodes, especially SJS/TEN, as presented in Table 3. The mucosal involvements of oral (92.11%), genital (92.11%) and ocular (55.26%) were statistically significantly reported in SJS/TEN patients. Oral and genital mucosal involvements were found in 24% of patients with DRESS; however, no mucosal involvement was found in AGEP patients.

Hospitalization, ICU admission, cost of treatment during SCARs episode and discharge status

The average length of hospital stay for SCARs treatment was 10.19 ± 11.23 (ranging from 2 to 81) days, in which the longest average length of hospital stay was reported in the TEN patients (15.20 ± 12.52 days) followed by SJS/TEN overlap and SJS. Moreover, the average length of hospital stays of all SJS/TEN patients was statistically significantly higher than DRESS and AGEP patients. For DRESS and AGEP, the average length of hospital stay was 6.72 ± 3.75 days and 3 days, respectively (Table 3). In consistent with the length of hospital stay, the cost of treatment was statistically significantly difference when compared among phenotypes of SCARs in which those of TEN was the highest among the other phenotypes, followed by SJS/TEN overlap, SJS, DRESS and AGEP. Only patients with TEN (5 cases, 100%), SJS/TEN overlap (2 cases, 40%) or SJS (3 cases, 10.71%) were admitted in intensive care unit (ICU), that was statistically significant difference when compared with DRESS and AGEP. Most of SCARs patients (93.75%) were discharged from the hospital with fully recovery status. Only one patient who had chronic kidney disease as underlying disease died in the hospital from sepsis with hypovolemic shock, which may be complications from TEN induced by allopurinol (SCORTEN on admission as 4). All data are shown in Table 3.

Disease severity of SCARs

In this study, the disease severity was evaluated for only SJS/TEN cases by using SCORTEN on admission. The results from all SJS/TEN cases showed that the average SCORTEN on admission was 1.5 ± 1.13. Most of SJS/TEN cases (20 cases, 52.63%) had the SCORTEN on admission as 0-1, followed by 2 (11 cases, 28.95%), 3 (5 cases, 13.16%) and 4 (2 cases, 5.26%). Moreover, the average SCORTEN on admission for TEN cases was significantly higher than SJS cases (2.60 ± 0.89 vs 1.25 ± 1.04, P = 0.0333) in which SCORTEN for TEN cases ranged from 2-4, for SJS/TEN overlap ranged from 1-4 and for SJS ranged from 0-3.

Treatment of SCARs

For the treatment of SCARs, prednisolone (systemic corticosteroid) was administered in 88 % of DRESS, 100% of AGEP, 32.14% of SJS, and 60% of SJS/TEN overlap. While dexamethasone was administered in 16 % of DRESS, 14.29% of SJS, and 40% of SJS/TEN overlap. Cyclosporin A was administered in 50% of SJS, 60% of SJS/TEN overlap and 40% of TEN. N-Acetylcysteine was administered in 78.57% of SJS, 80% of SJS/TEN overlap and 100% TEN. While intravenous immunoglobulin (IVIg) was administered only in TEN and SJS/TEN overlap cases. A combination of N-Acetylcysteine, cyclosporin A, and IVIg were prescribed only in patients diagnosed with SJS/TEN as shown in Table 4.

More than 75% of SJS/TEN cases regardless of SCORTEN score were prescribed with N-Acetylcysteine. Systemic corticosteroids were prescribed only in SJS/TEN patients with SCORTEN lower than or equal 2. IVIg was significantly prescribed in SJS/TEN patients with SCORTEN equal 4 (100%) when compared with patients who have SCORTEN lower 4 (P = 0.0124). Data was presented in Table 5.

Table 1 Demographic and clinical data of the drug-induced SCARs patients

Characteristics	SJS (n = 28)	SJS/TEN overlap (n = 5)	TEN (n = 5)	Total SJS/TEN (n = 38)	DRESS (n = 25)	AGEP (n = 1)	Total SCARs (n = 64)
Age, years							
Mean±SD	52.43±14.72	38.60±24.89	61.20±19.51	51.76±17.38	49±19.82	40	50.50±18.18
Median [range]	52.50 [29-84]	34 [17-81]	74 [32-75]	51.50 [17-84]	50 [20-84]	NA	50.50 [17-84]
Gender, n (%)							
Male	17 (60.71)	2 (40)	3 (60)	22 (57.89)	11 (44)	NA	33 (51.46)
Female	11 (39.29)	3 (60)	2 (40)	16 (42.11)	14 (56)	1 (100)	31 (48.44)
Comorbidities, n (%)							
Chronic kidney disease	2 (7.14)	NA	1 (20)	3 (7.89)	5 (20)	NA	8 (12.50)
Cardiovascular diseases							
Dyslipidemia	1 (3.57)	NA	NA	1 (2.63)	1 (4)	NA	2 (3.13)
Hypertension	7 (25)	NA	1 (20)	8 (21.05)	5 (20)	1 (100)	14 (21.88)
Atrial fibrillation	NA	NA	NA	NA	1 (4)	NA	1 (1.56)
Diabetes mellitus	6 (21.43)	1 (20)	1 (20)	8 (21.05)	2 (8)	1 (100)	11 (17.19)
Gout	3 (10.71)	1 (20)	1 (20)	5 (13.16)	5 (20)	NA	10 (15.63)
Neurological disorders							
Epilepsy	3 (10.71)	1 (20)	1 (20)	5 (13.16)	3 (12)	NA	8 (12.50)
Neuropathic pain	NA	NA	NA	NA	1 (4)	NA	1 (1.56)
Infections							
HIV infection	7 (25)	2 (40)	1 (20)	10 (26.32)	6 (24)	NA	16 (25)
Pulmonary tuberculosis	2 (7.14)	NA	1 (20)	3 (7.89)	NA	NA	3 (4.69)
Autoimmune diseases							
Systemic lupus erythematosus	2 (7.14)	NA	NA	2 (5.26)	NA	1 (100)*	3 (4.69)
Systemic sclerosis	NA	NA	1 (20)*	1 (2.63)	NA	NA	1 (1.56)
Liver impairment	NA	NA	1 (20)*	1 (2.63)	NA	NA	1 (1.56)

*$p < 0.05$, statistically significant when compared among phenotypes of SCARs; NA, not available.

Table 2 List of causative drugs for each phenotype of drug-induced SCARs

Drug class	SJS (n = 28)	SJS/TEN overlap (n = 5)	TEN (n = 5)	Total SJS/TEN (n = 38)	DRESS (n = 25)	AGEP (n =1)	Total SCARs (n = 64)
Antimicrobial agents	**16 (57.14)**	**3 (60)**	**2 (40)**	**21 (55.26)**	**9 (36)**	**1 (100)**	**31 (48.43)**
Co-trimoxazole	7 (25)	2 (40)	1 (20)	10 (26.32)	5 (20)	0	15 (23.44)
Ceftriaxone	0	1 (20)	1 (20)	2 (5.26)	1 (4)	0	3 (4.69)
Amoxicillin/clavulanic acid	0	0	0	0	2 (8)	0	2 (3.13)
Azithromycin	0	0	0	0	1 (4)	0	1 (1.56)
Ceftazidime	1 (3.57)	0	0	1 (2.63)	0	0	1 (1.56)
Colistin	1 (3.57)	0	0	1 (2.63)	0	0	1 (1.56)
Doxycycline	1 (3.57)	0	0	1 (2.63)	0	0	1 (1.56)
Fosfomycin	1 (3.57)	0	0	1 (2.63)	0	0	1 (1.56)
Meropenem	1 (3.57)	0	0	1 (2.63)	0	0	1 (1.56)
Norfloxacin	0	0	0	0	0	1 (100)	1 (1.56)
Ofloxacin	1 (3.57)	0	0	1 (2.63)	0	0	1 (1.56)
Streptomycin	1 (3.57)	0	0	1 (2.63)	0	0	1 (1.56)
Tetracycline	1 (3.57)	0	0	1 (2.63)	0	0	1 (1.56)
Vancomycin	1 (3.57)	0	0	1 (2.63)	0	0	1 (1.56)
Anticonvulsant drugs	**5 (17.86)**	**1 (20)**	**2 (40)**	**8 (21.05)**	**7 (28)**	**0**	**15 (23.44)**
Phenytoin	3 (10.71)	0	1 (20)	4 (10.53)	4 (16)	0	8 (12.50)
Carbamazepine	2 (7.14)	0	1 (20)	3 (7.89)	2 (8)	0	5 (7.81)
Levetiracetam	0	0	0	0	1 (4)	0	1 (1.56)
Sodium valproate	0	1 (20)	0	1 (2.63)	0	0	1 (1.56)
Urate lowering agent (allopurinol)	**4 (14.29)**	**1 (20)**	**1 (20)**	**6 (15.79)**	**6 (24)**	**0**	**12 (18.75)**
Antituberculosis drugs	**0**	**0**	**0**	**0**	**2 (8)**	**0**	**2 (3.13)**
Ethambutol	0	0	0	0	1 (4)	0	1 (1.56)
Rifampicin	0	0	0	0	1 (4)	0	1 (1.56)
Antiviral agents (efavirenz)	**1 (3.57)**	**0**	**0**	**1 (2.63)**	**1 (4)**	**0**	**2 (3.13)**
NSAIDs (piroxicam)	**1 (3.57)**	**0**	**0**	**1 (2.63)**	**0**	**0**	**1 (1.56)**
PPIs (omeprazole)	**1 (3.57)**	**0**	**0**	**1 (2.63)**	**0**	**0**	**1 (1.56)**

NSAIDs, non-steroidal anti-inflammatory drugs; PPIs, proton pump inhibitors

Table 3 Clinical characteristics and outcomes of drug-induced SCARs

Clinical characteristics and outcomes of SCARs	SJS (n = 28)	SJS/TEN overlap (n = 5)	TEN (n = 5)	Total SJS/TEN (n = 38)	DRESS (n = 25)	AGEP (n = 1)	Total SCARs (n = 64)
Onset of SCARs (days)							
Mean±SD	20.43±15.40	11.60±14.17	23±14.11	19.60±15.06	30.44±37.25	4	23.59±26.39
Median [range]	16 [1-56]	7 [1-36]	15 [10-42]	14 [1-56]	14 [2-138]	NA	17 [1-138]
Mucosal involvements, n (%)							
Oral	26 (92.86)*	5 (100)*	4 (80)*	35 (92.11)*	6 (24)	0	41 (64.06)
Ocular	12 (42.86)*	4 (80)*	5 (100)*	21 (55.26)*	1 (4)	0	22 (34.38)
Genital	26 (92.86)*	5 (100)*	4 (80)*	35 (92.11)*	6 (24)	0	41 (64.06)
Length of hospital stay (days)							
Mean±SD	11.89±15.07	14.40±7.02*	15.20±12.52*	12.66±13.77	6.72±3.75	3	10.19±11.23
Median [range]	8 [3-81]	16 [4-23]	10 [6-37]	9 [3-81]	6 [2-15]	NA	7 [2-81]
ICU admission, n (%)							
Yes	3 (10.71)	2 (40)*	5 (100)*	10 (26.32)*	0	0	10 (15.63)
Cost of treatment during hospitalization (Baht)							
Mean ±SD	54,455.46** ±109,991.69	165,614.60* ±191,950.48	279,883.80*** ±159,122.93	98,743.29* ±148,565.10	16,654.64 ±11,077.54	5,701	65,223.63 ±121,158.83
Median [range]	24,842.50 [2,241-518,652]	56,199 [9,413-470,595]	219,269 [175,336-560,338]	32,784.5 [2,241-560,338]	12,738 [4,154-44,154]	NA	20,304 [2,241-560,338]
Discharge status, n (%)							
Improved	27 (96.43)	5 (100)	3 (60)	35 (92.11)	24 (96)	1 (100)	60 (93.75)
Against medical advice	1 (3.57)	0	1 (20)	2 (5.26)	1 (4)	0	3 (4.69)
Death	0	0	1 (20)	1 (2.63)	0	0	1 (1.56)

*p < 0.05, statistically significant when compared with DRESS or AGEP, **p < 0.05, statistically significant when compared with DRESS or TEN, ***p < 0.05, statistically significant when compared with SJS, DRESS or AGEP

Table 4 Treatment of all phenotypes of drug-induced SCARs

Treatment with systemic pharmacotherapy, n (%)	SJS (n = 28)	SJS/TEN overlap (n = 5)	TEN (n = 5)	Total SJS/TEN (n = 38)	DRESS (n = 25)	AGEP (n = 1)	Total SCARs (n = 64)
Prednisolone	9 (32.14)	3 (60)	0	12 (31.58)	22 (88)*	1 (100)	35 (54.69)
Dexamethasone	4 (14.29)	2 (40)	0	6 (15.79)	4 (16)	0	10 (15.63)
N-Acetylcysteine	22 (78.57)	4 (80)	5 (100)	31 (81.58)**	0	0	31 (48.44)
Cyclosporin A	14 (50)	3 (60)	2 (40)	19 (50)	0	0	19 (29.69)
Intravenous Immunoglobulin (IVIg)	0	2 (40)	4 (80)***	6 (15.79)	0	0	6 (9.38)

*p < 0.05, statistically significant when compared with total SJS/TEN

**p < 0.05, statistically significant when compared with DRESS or AGEP

***p < 0.05, statistically significant when compared with SJS or SJS/TEN overlap

Table 5 Treatment of SJS/TEN based on SCORTEN

	SCORTEN for SJS/TEN cases (n = 38)			
Treatment with systemic pharmacotherapy, n (%)	**SCORTEN = 0-1 (n = 20)**	**SCORTEN = 2 (n = 11)**	**SCORTEN = 3 (n = 5)**	**SCORTEN = 4 (n = 2)**
Prednisolone	7 (35)	5 (45.45)	0	0
Dexamethasone	4 (20)	2 (18.18)	0	0
N-Acetylcysteine	15 (75)	9 (81.82)	5 (100)	2 (100)
Cyclosporin A	12 (60)	3 (27.27)	3 (60)	1 (50)
Intravenous Immunoglobulin (IVIg)	1 (5)	2 (18.18)	1 (20)	2 (100)*

*p < 0.05, statistically significant when compared among SCORTEN

Discussion

In this present study, the epidemiology of drug-induced SCARs including the causative drugs, clinical characteristics, treatment, and outcomes from SCARs episodes were determined in 64 patients who were diagnosed with drugs-induced SCARs and admitted in a regional hospital in Northeastern region of Thailand between 2019 and 2023.

Results from the present study revealed that SJS is the most common SCAR phenotype, consistent with previous studies in adult Northeastern Thai population[9], Thai patients from six tertiary medical centers across Thailand[10] and Chinese population[18]. However, a contrasting result was reported in a study involving pediatric Thai patients, which found that DRESS was the most prevalent phenotype in that population. Consistent with previous studies in the Thai population[9], comorbidities such as hypertension, diabetes mellitus, gout, epilepsy, and chronic kidney disease were frequently observed in both SJS/TEN and DRESS phenotypes. However, HIV infection emerged as the most prevalent comorbidity in this study population, a notable deviation from previous

study[9]. This variation may be influenced by demographic, geographic, or healthcare-related factors.

The major causative drugs of SCARs identified in this study population were antimicrobial agents, followed by anticonvulsant drugs, and urate lowering agent (allopurinol), When focusing on each phenotype of SCARs, co-trimoxazole was the most common causative drug of SJS/TEN, followed by allopurinol, phenytoin and carbamazepine, This finding differs from previous studies conducted in Thai populations[9,10], which consistently identified allopurinol as the primary causative drug associated with SJS/TEN. However, the top four causative drugs of SJS/TEN identified in this study were consistent with those reported in previous study on the Thai population[9], these causative drugs included allopurinol, co-trimoxazole, phenytoin, and carbamazepine in previous study[9]. On the other hand, the study on the medication risk of SJS/TEN in Asians reported that carbamazepine was the most common cause of SJS/TEN, followed by allopurinol, phenytoin, and lamotrigine[8]. For drug-induced DRESS in this present study, allopurinol was identified as the most common causative drug of DRESS, followed by co-trimoxazole, phenytoin, and carbamazepine. In contrast, a previous study on the Thai population reported phenytoin, allopurinol, co-trimoxazole, and phenobarbital as the most common causative drugs of DRESS, respectively[9]. The causative drug in one AGEP patient enrolled in this study was norfloxacin, which in line with previous reports in several populations including Thai, that revealed antibiotics, especially β-lactam antibiotics and quinolones, as the common causative drugs of AGEP[2,11,19,20]. It should be noted that the Naranjo algorithm was solely used for the assessment of the causative drug in all SCARs cases in this study.

The average exposure time to causative drug until the first signs of SCARs (onset) varies depending on phenotypes of SCARs in which DRESS showed the longest onset, whereas, AGEP showed the shortest onset among other phenotypes. This finding was consistent with the previous reports in several population including Thais[7,9] and previous studies of SCARs associated with various drugs, including co-trimoxazole[21], allopurinol[22], phenytoin[23], carbamazepine[24], or beta-lactam antibiotics[20], all of which consistently reported the longest latency period for DRESS among SCAR phenotypes. The mucosal involvements were significantly noted in the SJS/TEN patients. Moreover, the length of hospital stay, the percentage of ICU admission as well as the cost of treatment during hospitalization were significantly higher in the treatment of patients with SJS/TEN, particularly TEN and SJS/TEN overlap, when compared with DRESS and AGEP. The longest length of hospital stay and highest cost of treatment were observed in TEN patients. In addition, the patients with TEN showed the significantly highest severity based on SCORTEN on admission. The SCORTEN for TEN cases in this study ranged from 2-4, therefore, the predicted mortality rate was about 12.1% - 58.3%[5]. These findings suggest that the SJS/TEN patients with high disease severity, as indicated by SCORTEN, require longer length of hospital and higher cost of treatment, therefore, early diagnosis of SJS/TEN is crucial in slowing disease progression, which can improve clinical outcomes and potentially reduce hospital stay duration, healthcare costs, and mortality rates.

For the management of SCARs, early diagnosis, prompt withdrawal of the causative drugs and supportive care are very important[2]. Treatment of SCARs varies according to clinical manifestation and severity of the disease. Immunomodulatory therapy is required for controlling the immune reaction and inflammation in SCARS patients. In the clinical practice, immunomodulating treatments for SJS/TEN include systemic corticosteroids, cyclosporin A and IVIg[2], in addition, TNF inhibitors, especially etanercept, showed the beneficial effects in the treatment of SJS/TEN[25,26]. While systemic corticosteroids are the primary treatment for both DRESS and AGEP[2,27]. For the

treatment of SJS/TEN in this study, systemic corticosteroids were prescribed to only SJS or SJS/TEN overlap patients with SCORTEN lower than or equal 2, while cyclosporin A and IVIg were mostly prescribed to patients with SJS/TEN who have more severity of disease based on SCORTEN, particularly that IVIg were significantly prescribed to SJS/TEN patients with SCORTEN greater than or equal 4, suggesting that clinicians may prefer this immunomodulatory therapy for cases with higher mortality risk. Previous studies have reported the benefits of cyclosporin A and IVIg in reducing mortality rates[28,29]. However, it is important to note that there are no established clinical guidelines that define treatment selection for SJS/TEN based on SCORTEN. Despite this, SCORTEN is widely used in the clinical practice for assessing disease severity and guiding treatment decisions[28-30]. Moreover, N-acetylcysteine were used in most of all SJS/TEN patients in this study. N-acetylcysteine is used as a precursor of glutathione (GSH) synthesis, antioxidant, mucolytic agent, and anti-inflammatory agent. The evidence from previous reports demonstrated the beneficial effects of the use of N-acetylcysteine combined with other immunomodulating agents in SJS/TEN management[31]. In this study, the rate of discharge with discharge against medical advice was 4.69% (3 out of 64 patients), potentially due to the underlying conditions of the patients. The observed mortality rate at discharge was 1.56% (1 out of 64 patients, allopurinol-induced TEN with an admission SCORTEN of 4). However, the observed mortality rate is notably lower than the predicted mortality rate reported in previous study (58.3% for a SCORTEN of 4)[5], suggesting that the treatment provided was effective in improving patient outcomes.

This study has some limitations. First, the sample size was relatively small, and patients with generalized bullous fixed drug eruption, one of drug-induced SCARs phenotypes, were not included due to the rarity of this condition in the study population. Second, the retrospective design may have led to missing or incomplete data, particularly regarding laboratory results. Third, as the data were collected from a single regional hospital, the findings may not be generalizable to other healthcare settings. Future multicenter studies with larger and more diverse populations are warranted to validate and extend these findings.

Conclusion

In conclusion, this study provides valuable information on the causative drugs, characteristics, treatment, and outcomes of SCARs, which can be useful in clinical practice by increasing awareness when prescribing common causative drugs, enabling earlier diagnosis, accurate prognosis, and proper management, ultimately improving patient safety.

Acknowledgements

The authors appreciate the support from the staff members at the Division of Dermatology, Department of Internal Medicine, Khon Kaen Hospital and from KKU SCARs research group, Department of Pharmacology, Faculty of Medicine, Khon Kaen University.

Conflict of interest

The authors have no conflict of interest to declare.

Source of funding

This work was supported by grants from the Health System Research Institute under Genomics Thailand Strategic Fund (HSRI. 65-038).

Author contributions

WA and NN designed the study. WA enrolled the patients. WA, NN, and OP reviewed and collected the clinical data. WA NN and WT analyzed and interpreted the data. WA, NN, and WT drafted the manuscript. All authors have read and approved the final version of the manuscript.

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