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ORIGINAL RESEARCH

Incidence, causative drugs, and economic consequences of drug-induced SJS, TEN, and SJS–TEN overlap and potential drug–drug interactions during treatment: a retrospective analysis at an Indonesian referral hospital

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Background: Stevens–Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) are acute life-threatening adverse drug reactions (ADRs) that are commonly caused by medications. Apart from their contribution to morbidity and mortality, these diseases may also present substantial consequences on health care resources. In this study, we aimed to identify the incidence, causative drugs, and economic consequences of these serious ADRs and potential drug–drug interactions (DDIs) during treatment.

Methods: A retrospective study that included 150 patients diagnosed with drug-induced SJS, SJS–TEN overlap, and TEN, from 2009 to 2013 in a referral hospital in West Java Province, Indonesia, was conducted to analyze the causative drugs, cost of illness (COI) as a representation of economic consequences, and potential DDIs during treatment.

Results: The results showed that analgesic–antipyretic drugs were the most frequently implicated drugs. The COIs for SJS, SJS–TEN overlap, and TEN patients were 119.49, 139.21, and 162.08 US dollars per day, respectively. Furthermore, potential DDIs with several therapeutic medications and corticosteroids used to treat SJS, SJS–TEN overlap, and TEN were also identified.

Conclusion: This study showed that analgesic–antipyretic was the major causative drug which contributed to SJS, SJS–TEN overlap, and TEN. Furthermore, our results also showed that SJS, SJS–TEN overlap, and TEN may cause considerable financial consequences to patients.

Keywords: Stevens–Johnson syndrome, toxic epidermal necrolysis, adverse drug reactions, cost of illness

Introduction

Stevens–Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) are acute life-threatening adverse drug reactions (ADRs) characterized by epidermal detachment and mucositis.[1] The basic difference between SJS and TEN is the percentage of body surface affected, and SJS affects <10% of the body surface, SJS–TEN overlap involves 10%–30% of the body surface, and TEN affects >30% of the body surface area.[2,3] The incidence varies from 1 to 6 cases and 0.4 to 1.2 cases per million annually for SJS and TEN, respectively.[4–6] However, the incidence is higher among people living with HIV/AIDS.[7]

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Drugs are identified as the main etiologic agents of SJS, TEN, and SJS–TEN overlap syndrome. Based on RegisSCAR/EuroSCAR registries, the highest risk drugs include allopurinol, carbamazepine, cotrimoxazole, and other anti-infective sulfonamides, sulfasalazine, lamotrigine, nevirapine, oxicam-type non-steroidal anti-inflammatory drugs (NSAIDs), phenobarbital, and phenytoin. Moderate-risk drugs include cephalosporins, macrolides, quinolones, tetracyclines, and acetic acid-type NSAIDs. Low-risk drugs, that in previous studies, were not associated with a measurable risk, including beta-blockers, angiotensin-converting enzyme inhibitors, calcium channel blockers, sulfonamide-based thiazide diuretics, sulfonylurea anti-diabetics, insulin, and propionic acid–type NSAIDs.[8,9]

Despite the fact that the incidence of SJS or TEN is acute life-threatening, the condition may also lead to significant financial consequences for the patients.[10] Therefore, identification and withdrawal of drugs suspected to cause SJS or TEN are important.[11] In Indonesia, however, little work has been conducted to identify the prevalence, causative drugs, and economic consequences caused. Accordingly, it is important to explore the best strategy to find as many relevant studies as possible. Thus, this study was aimed to identify the number of incidence, causative drugs, economic consequences, and potential drug–drug interaction (DDI) during treatment of these serious ADRs.

Methods

Data collection and study populations

We conducted a retrospective study in a referral hospital in West Java Province, the most populous Indonesian province, that is covered with 46.7 million population.[12] Medical records from patients diagnosed with drug-induced SJS (ICD10 code L50.1), TEN (L50.2), or SJS–TEN overlap (L50.3) syndrome from January 1, 2009, to December 31, 2013, were recalled and included in the study. A data collection sheet was designed for the purpose of organizing collected data from patient records. Data included patient demographics, disease progression, duration of hospital stay, detailed treatment regimen, and suspected causative drugs as specifically mentioned in medical records by treating physicians. Incomplete patient records and records of patients referred with SJS, TEN, or SJS–TEN overlap syndrome from other hospitals were excluded from the study. Incomplete patient records that excluded were due to insufficient data and improper record, that is missing of suspected causative drug from the treating physicians, and incomplete medical treatment records. Two authors (RA and DPD) independently assessed the medical record for inclusion to the study. Differences were discussed and consensus reached.

Ethical approval for the study was obtained from the Ethical Committee for Health Research of Hasan Sadikin Hospital, Bandung, Indonesia No: LB.04.01/A05/EC/536/XII/2014. The study was conducted according to the guidelines of the Declaration of Helsinki. Written informed consent was not required because this was a retrospective observational study. No medical interventions were performed during the study. All ethical considerations were followed. Patient files were processed anonymously. No personal data were collected.

Analysis of economic consequences

The economic consequences of SJS, TEN, and SJS–TEN overlap were calculated using cost of illness (COI) for each patient. A societal perspective was applied in this study by considering the total direct medical cost and indirect cost of lost productivity. The direct medical cost was calculated by considering the price of all medications received, expenses (preparation and administrative costs, monitoring costs, and the costs of treatment for adverse events and treatment failures), the cost of action, and the hospital room rate (including fees for doctors, nurses, pharmacies, and nutritionists that differ depending on the severity and treatment received by each patient). The potential loss of productivity was calculated using a report from the Indonesian Statistical Agency for average monthly income of people living in Bandung City, Indonesia,[13] that adjusted to the total length of hospital stay of each patient.

Currency was converted from the Indonesian rupiah (IDR) to the US dollar (USD) using the World Bank's purchasing power parity (PPP) conversion factor, which is the number of units of a country's currency required to buy the same amount of goods and services in the domestic market as the USD would buy in the USA.[14]

Analysis of drug interaction

The analysis of potential DDIs was performed to analyze the interactions of SJS/TEN treatment with the drugs suspected of being the cause of SJS/TEN and interactions of concomitant therapy between SJS/TEN treatment with drugs used to treat the original disease not related to SJS/TEN. Identification of DDIs was performed with Truven Health Analytics Micromedex®, a registered subscription database, and Drugs.com™ and Medscape.com™, 2 free databases. Micromedex provides reference information for drug management for diseases and conditions, as well as toxicology and patient education. Micromedex

identifies potential DDIs, including the mechanism of DDIs, potential adverse reactions, their clinical consequences, and level of documentation available for the interaction (excellent: controlled study have clearly established; good: documentation strongly suggests the interactions; fair: available documentations were poor).[15] Drugs.com is a free database powered by Wolters Kluwer Health, the American Society of Health-System Pharmacists, Cerner Multum, and Micromedex, which are leading medical information databases.[15] Medscape.com provides online medical information and educational tools,[16] including a drug interaction checker.

Results

Number of incidence

From the records of 150 patients diagnosed with SJS, SJS–TEN overlap, and TEN during 2009–2013, a total of 101 medical records were included in this study. The details of the selection process are shown in Figure 1. The demographics of the patients included in this study are shown in Table 1.

Economic consequences

The total economic loss from the 101 cases of SJS, SJS–TEN overlap, and TEN during the study period was estimated at 131,763.82 USD, including 77,786.64, 29,179.29, and 24,797.89 USD from SJS, SJS–TEN overlap, and TEN, respectively. For SJS, SJS–TEN overlap, and TEN, the average cost per patient was 1,111.24, 1,823.71, and 1,653.12 USD, respectively, and the average direct cost per patient was 974.86, 1,630.91, and 1,504.07 USD, respectively. A detailed breakdown of the cost calculation and average spending per patient per day for SJS, SJS–TEN overlap, and TEN can be seen in Table 2.

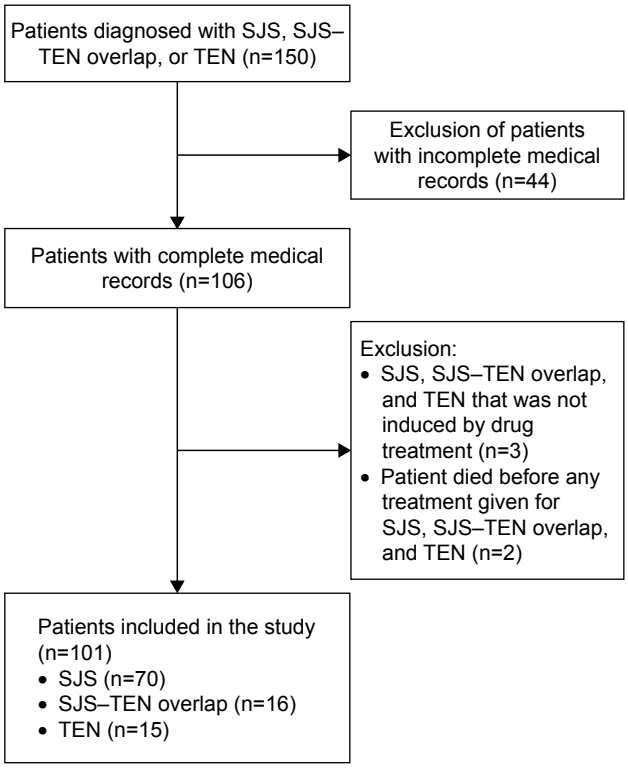

Figure 1 Detailed medical record selection process.
Abbreviations: SJS, Stevens–Johnson syndrome; TEN, toxic epidermal necrolysis.

Causative drugs

Each drug implicated in SJS, SJS–TEN overlap, and TEN in the study can be seen in Table 3. As shown, analgesic–antipyretic drugs (acetaminophen) were reported most frequently, followed by antibiotics (amoxicillin, cotrimoxazol, and ciprofloxacin), tuberculosis drugs (rifampicin, ethambutol, isoniazid, and pyrazinamide), anti-HIV medications (nevirapine, lamivudine, and zidovudine), and NSAIDs (mefenamic acid, ibuprofen, and aspirin). In Table 3, the implicated drugs were compared to other reports from Japan,[17] Europe and Israel,[18] France,[19] sub-Saharan Africa,[20] and Senegal.[21]

Potential DDIs

The results of DDI analysis from 3 of the databases showed discrepancies in the classification of severity and mechanism of interaction (Table 4A and B). However, we found 29 cases identified by all 3 databases for potential interactions of SJS/TEN treatment with the drugs suspected of being the cause of SJS/TEN and 87 cases identified by all 3 databases for potential interaction of concomitant therapy between SJS/TEN treatment with drugs used to treat the original disease not related to SJS/TEN. The most common potential DDIs of corticosteroids with the drugs suspected of being the cause of SJS/TEN identified by the 3 databases were dexamethasone–rifampicin (24.14%), dexamethasone–ciprofloxacin (20.69%), dexamethasone–ibuprofen (20.69%), dexamethasone–mefenamic acid (17.24%), and dexamethasone–aspirin (10.34%). Meanwhile, the most common potential DDIs of concomitant treatment of corticosteroids with drugs used to treat the original disease not related to SJS/TEN were dexamethasone–ofloxacin (12.64%), dexamethasone–levofloxacin (10.34%), dexamethasone–ciprofloxacin (8.05%), dexamethasone–efavirenz (6.90%), and dexamethasone–phenobarbital (6.90%).

Discussion

The drugs most frequently implicated in cases of SJS, SJS–TEN overlap, and TEN in our study were analgesic–antipyretic

Table 1 Demographic characteristics of patients included in this study

Demographic parameters	SJS (n=70)	SJS–TEN overlap (n=16)	TEN (n=15)
Gender			
Male	33	8	5
Female	37	8	10
Age (years)	30.15±16.45	26.75±18.65	25.45±15.82
LoS (days)	9.33±6.68	13.19±6.91	10.20±7.66

Note: Data presented as number or mean ± SD.
Abbreviations: SJS, Stevens–Johnson syndrome; TEN, toxic epidermal necrolysis; LoS, length of hospital stay.

(Table 3). Although not in the top 5 of drugs most implicated in this study, antiepileptic carbamazepine counted for up to 3.92% of all the drugs implicated. Carbamazepine-induced SJS/TEN is reported to be associated with HLA allele B*1502,[22] whose frequency has been reported to be as high as 11.6% in Western Javanese population.[23] Therefore, this should also be seriously considered, especially as carbamazepine also used in off-label prescription.[24]

It has been reported that the treatment of ADR-related diseases requires substantial financial resources, as many countries may spend 15%–20% of hospital budgets for this purpose.[25,26] Considering the potentially serious consequences, SJS, SJS–TEN overlap, and TEN may have a significant clinical and economic impact on patients. A previous study reported that patients with ADRs may stay in the hospital 12 days longer than those without ADRs.[27] This can significantly affect those in developing countries due to the damaging effects of ADR-related diseases on the socioeconomic progress of those countries. SJS, SJS–TEN overlap, and TEN will increase treatment costs due to prolonged hospital stays, additional clinical investigations, and treatments. As seen in Table 2, the COI of SJS patients in our study was 119.49 USD per day for only SJS-related medication, not the cost of treatment of their primary diagnosis before SJS diagnosis. Meanwhile, with the involvement of more body surface area, the daily COI for SJS–TEN overlap and TEN patients increases to 139.21 and 162.08 USD, respectively. These are higher than a previous report from Gujarat, India, that reported 15.16, 18.04, and 22.96 USD per day for SJS, SJS–TEN overlap, and TEN, respectively, after converted to USD using the World Bank's PPP conversion factor.[10,14] The Gujarat study, however, only calculated the cost of medications, diagnosis, and consumables used during the hospital stay.

Table 2 Economic cost calculation and average spending per patient per day for each case of SJS, SJS–TEN overlap, and TEN in this study

	SJS	SJS–TEN overlap	TEN
Length of hospital stay (days)	9.3	13.1	10.2
Direct medical cost			
Prescribed medicine related to SJS, SJS–TEN overlap, and TEN treatment (USD)	163.04	280.49	279.39
Medical treatment cost (USD)	117.32	249.17	284.07
Other medical supporting cost (USD)	216.39	426.85	418.25
Hospital stay and administration (USD)	478.11	674.40	522.37
Indirect medical cost			
Potential productivity lost (USD)	136.38	192.80	149.12
Total COI (USD)	1,111.24	1,823.71	1,653.20
COI per day of hospital stay (USD)	119.49	139.21	162.08

Abbreviations: SJS, Stevens–Johnson syndrome; TEN, toxic epidermal necrolysis; USD, US dollar; COI, cost of illness.

The average hospital stay in this study was ~9.3, 13.1, and 10.2 days for SJS, SJS–TEN overlap, and TEN, respectively. The number of hospital stays may associate to the different levels of severity and complexity of SJS, SJS–TEN overlap, and TEN patients. Patients with TEN have a more severe disease and are likely to have longer hospital stay than patients with SJS. However, these findings were less significant than those reported in a previous study in Thailand.[28] In particular, a longer hospital stay was observed among SJS–TEN patients than among TEN patients in our study. This finding could be explained by the fact that 8 of 15 TEN patients were died within a short period of time, thus resulting in a shorter average hospital stay than SJS–TEN patients. This result is in line with the latest study from Thailand.[29] In contrast to the average hospital stay in this study, TEN patients had the highest COI of the patients studied. This result is probably because TEN patients were likely to be more complicated recoveries than SJS and SJS–TEN patients.

There is currently no specific treatment for TEN or SJS because of their complex pathogenesis. Although systemic corticosteroids and intravenous immunoglobulin are controversial, they are still the main treatment methods in many countries,[30] including Indonesia. In our study, most cases were treated with corticosteroids. Although corticosteroids are controversial for the treatment of SJS and TEN due to the reports on the increased risk of secondary infection and delay in epithelialization,[31–33] they are still beneficial when started early and in an appropriate dose range.[34] The use of corticosteroids may be based on the idea that they may inhibit immunological responses by suppressing interferon gamma-mediated apoptosis and the functions of cytotoxic T lymphocytes.[35] The corticosteroids, however, have to be used cautiously for the treatment of SJS, SJS–TEN overlap, and TEN, as in our study, they have the potential for DDIs with medicines used to treat the primary disease. The most common potential DDIs of corticosteroids found in this

Table 3 Drugs implicated in SJS, SJS–TEN overlap, and TEN, their incidence in this study, and comparison with other reports

	Our study	Other reports				
	Indonesia (2009–2013)	Yamane et al, Japan (2000–2006)[17]	Halevy et al, Europe and Israel (1997–2001)[18]	Gueudry et al, France (1994–2002)[19]	Saka et al, Africa (2000–2010)[20]	Mame Thierno et al, Senegal (1995–2000)[21]
Total no of cases	101	117	379	159	177	38
SJS	70	52	134	56	129	0
SJS–TEN overlap	16	0	136	59	11	0
TEN	15	65	109	44	37	38
Death rate (%)	10.9	4.2	21	18.9	12.4	60
Drugs implicated						
1	Analgesic–antipyretic (13.40%)	Anticonvulsants	Allopurinol	Antibiotics	Sulfonamides	Tuberculosis drugs
2	Antibiotics (11.76%)	Antibiotics	Carbamazepine	Anticonvulsants	Nevirapine	Sulfonamides
3	Tuberculosis drugs (9.80%)	NSAIDs	Cotrimoxazole	NSAIDs	Tuberculosis drugs	Anticonvulsants
4	Anti-HIV (6.54%)	Allopurinol	Nevirapine	Allopurinol	NSAIDs	NSAIDs
5	NSAIDs (5.23%)	Antitussive	Phenobarbital	–	Anticonvulsants	Aminopenicillins

Note: The "–" indicates that this reference only provided 4 types of drugs.
Abbreviations: SJS, Stevens–Johnson syndrome; TEN, toxic epidermal necrolysis; NSAIDs, non-steroidal anti-inflammatory drugs.

Table 4 Results of DDI analysis of (**A**) corticosteroids with the drugs suspected of being the cause of SJS/TEN and (**B**) concomitant treatment of corticosteroids with drugs used to treat the original disease not related to SJS/TEN, identified using the Micromedex, Drugs.com, and Medscape.com websites

	DDI databases		
	Micromedex	Drugs.com	Medscape.com
(A)			
Number of patients with potential DDIs	32 (31.68%)	42 (41.58%)	46 (45.54%)
Number of patients without potential DDIs	69 (68.32%)	59 (58.42%)	55 (54.46%)
Number of interactions	35	46	54
Severity			
Contraindicated	0	0	0
Major/serious	17 (48.57%)	6 (13.04%)	19 (35.19%)
Moderate/significant	18 (51.43%)	40 (86.96%)	35 (64.81%)
Minor	0	0	0
Mechanism			
Unknown	12 (34.29%)	30 (65.22%)	17 (31.48%)
Pharmacokinetic	8 (22.86%)	16 (34.78%)	33 (61.11%)
Pharmacodynamic	11 (31.43%)	0	4 (7.41%)
Pharmacokinetic/pharmacodynamic	4 (11.43%)	0	0
Onset			
Delay (after 24 hours)	18 (51.43%)	–	–
Rapid (until 24 hours)	0	–	–
Not specified	17 (48.57%)	–	–
Documentation		–	–
Excellent	6 (17.14%)	–	–
Good	17 (48.57%)	–	–
Fair	12 (34.29%)	–	–
(B)			
Number of patients with potential DDIs	49 (48.51%)	34 (33.66%)	27 (26.73%)
Number of patients without potential DDIs	52 (51.49%)	67 (66.34%)	74 (73.27%)
Number of interactions	113	250	268
Severity			
Contraindicated	0	0	0
Major/serious	25 (22.12%)	52 (20.80%)	9 (3.36%)
Moderate/significant	79 (69.91%)	126 (50.40%)	179 (66.79%)
Minor	9 (7.96%)	72 (28.80%)	80 (29.85%)

(*Continued*)

Table 4 (*Continued*)

	DDI databases		
	Micromedex	**Drugs.com**	**Medscape.com**
Mechanism			
Unknown	56 (49.56%)	83 (33.20%)	50 (18.66%)
Pharmacokinetic	36 (31.86%)	86 (34.40%)	153 (57.09%)
Pharmacodynamic	21 (18.58%)	77 (30.80%)	64 (23.88%)
Pharmacokinetic/pharmacodynamic	0	4 (1.60%)	1 (0.37%)
Onset			
Delay (after 24 hours)	72 (63.72%)	–	–
Rapid (until 24 hours)	5 (4.42%)	–	–
Not specified	36 (31.86%)	–	–
Documentation			
Excellent	48 (42.48%)	–	–
Good	31 (27.43%)	–	–
Fair	34 (30.09%)	–	–

Note: The "–" indicate Drugs.com and Medscape.com did not provide that data.
Abbreviations: DDI, drug–drug interaction; SJS, Stevens–Johnson syndrome; TEN, toxic epidermal necrolysis.

study were its interaction with fluoroquinolone antibiotics, which may increase risk of tendinitis and tendon rupture,[36] with phenobarbital, which may decrease the blood level and systemic effects of corticosteroids,[37] and with fluconazole, which may increase the blood level and systemic effect of corticosteroids.[38–40] Health care professionals should pay attention to this potential DDI during the treatment of SJS, SJS–TEN overlap, and TEN, as it will increase the financial burden of the patients that was already high due to these serious ADRs.

Our study, however, still have some limitations. Due to the nature of retrospective study, we cannot recognize the ethnic origin of the subjects included in this study. Thus, we cannot analyze any potential association between SJS, SJS–TEN overlap, and TEN to specific ethnic of origin and populational variances among ADRs and DDIs. Furthermore, there is also potential bias in the SJS misclassification, as erythema multiforme major, a disease usually not related to medications and with much better prognosis, is also often classified as SJS.[41] Although it was impossible to perform a retrospective reclassification, in our study we have minimized this misclassification bias by including only the drug-induced SJS in the study.

Conclusion

Treating physicians and pharmacists should also consider the potential DDIs between the medication given and the medication for other diseases that are independent from SJS, SJS–TEN overlap, and TEN treatments. Furthermore, our results also showed that SJS, SJS–TEN overlap, and TEN could present a considerable financial consequence to the patients.

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Disclosure

The authors report no conflicts of interest in this work.

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