INVITED ARTICLE

Epidemiology of Stevens–Johnson syndrome and toxic epidermal necrolysis in Southeast Asia

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Abstract

Stevens–Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) are severe life-threatening reactions characterized by epidermal detachment and mucositis. These reactions are predominantly drug-related. Although a wide spectrum of medications have been reported to be causal in these reactions, the international case–control SCAR (severe cutaneous adverse reactions)1 and EuroSCAR2 studies have shown that in Europe, the majority of reactions can be attributed to a group of high-risk drugs such as allopurinol, carbamazepine, phenytoin, lamotrigine, oxicam nonsteroidal anti-inflammatory drugs, sulfonamide antibiotics, and nevirapine.

In parallel, several epidemiological studies (both retrospective and prospective) have been conducted in Europe looking at the incidence of SJS/TEN. Initial hospital-based retrospective studies have estimated the incidence of SJS/TEN within Germany to be within 1–2 cases/million/year.3 It is now known that there is a strong genetic association between human leukocyte antigens and drug-induced SJS/TEN. These genetic associations are not only drug and phenotypic specific, but are also ethnic specific as well. The aim of this review is to summarize existing epidemiological data on SJS/TEN within Southeast (SE) Asia.

Introduction

Stevens–Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) are severe life-threatening reactions characterized by epidermal detachment and mucositis. These reactions are predominantly drug-related. Although a wide spectrum of medications have been reported to be causal in these reactions, the international case–control SCAR (severe cutaneous adverse reactions)1 and EuroSCAR2 studies have shown that in Europe, the majority of reactions can be attributed to a group of high-risk drugs such as allopurinol, carbamazepine, phenytoin, lamotrigine, oxicam nonsteroidal anti-inflammatory drugs, sulfonamide antibiotics, and nevirapine.

In parallel, several epidemiological studies (both retrospective and prospective) have been conducted in Europe looking at the incidence of SJS/TEN. Initial hospital-based retrospective studies have estimated the incidence of TEN in France and Germany to be 1.2 and 0.9 cases/million/year, respectively.3,4 Newer prospective population-based studies based on the German registry have estimated the incidence of SJS/TEN within Germany to be within 1–2 cases/million/year.5

It is now known that there is a strong genetic association between human leukocyte antigens and drug-induced SJS/TEN. These genetic associations are not only drug and phenotypic specific, but are also ethnic specific as well. The aim of this review is to summarize existing epidemiological data on SJS/TEN within Southeast (SE) Asia.

Geography of SE Asia

SE Asia is a diverse region made up of 10 member countries (Brunei, Cambodia, Indonesia, Laos, Malaysia, Myanmar, Philippines, Thailand, Singapore, and Vietnam). It covers a land area of 4.5 million km² and has a population of approximately 600 million people of diverse ethnicities.6 Many of the data on SJS/TEN in this region have been derived from publications originating from Malaysia, Philippines, Singapore, and Thailand and these will be summarized in this review.

Epidemiology of SJS/TEN in SE Asia

The incidence of SJS/TEN in SE Asia is largely undetermined. No prospectively epidemiological studies have been published. A retrospective hospital-based study has estimated the incidence of TEN in Singapore to be at least 1.4 cases/million.7 When considered as a whole, the prevalence of cutaneous adverse drug reactions (CADR) in hospitalized patients varies from 1.3 CADRs to 4.2 CADRs/1000 hospitalized patients in Singapore with severe cutaneous adverse reactions (SCAR) constituting 5–14% of these reactions.8,9 In Malaysia, the incidence of CADR is 0.86% among new patients assessed in a tertiary hospital and SJS/TEN account for 30% of these reactions.9

Drug causality

In SE Asia, based on published retrospective case series reported from 1984 to 2013 (overlapping publications have been excluded), the major culprit drugs implicated include carbamazepine (CBZ; 17%), allopurinol (15%), sulfonamide antibiotics (12%),
phenytoin (PHT; 9%), nonsteroidal anti-inflammatory drugs (8%), lamotrigine (2%), phenobarbital (1%), and β-lactam antibiotics (13%). The distribution of reported cases and causal drugs are summarized in Table 1 and Figure 1. High-risk drugs, as identified in the European studies, were also major culprits in SE Asia being the implicated drug in 64% of cases.1,2

Variations in SE Asia drug causality

CBZ and PHT induced SCAR

The proportion of CBZ and PHT-induced SJS/TEN in SE Asia is significantly higher, accounting for 26% of all cases (Figure 1), as opposed to 12% in European populations.20 Although variations in clinical practice, prescribing patterns, and incidence of disease may play a role, it is believed that pharmacogenetic variations between different ethnicities is a major factor.

Complementary medications

The use of traditional/complementary medications such as traditional Chinese medications and jamu—a form of Indonesian/Malay herbal preparation—is widespread within the region and is culturally acceptable and perceived to be safe due to its herbal origin. However, such medications are poorly regulated and the constituents of these medications are not always known. Complementary medications have been associated with 4% of cases in Singapore and 5% of reported cases from Malaysia (Dr M.M. Tang, Kuala Lumpur, Malaysia, personal communication) and reports of these medications being adulterated by phenylbutazone have been reported.21,22

Occupational trigger

Occupational exposure to trichloroethylene has occasionally been reported as a trigger of SJS/TEN and DRESS in SE Asia and Asia, with cases being reported in Singapore, Thailand, Philippines, Japan, Taiwan, and China.23–25 Trichloroethylene is an organic solvent that is used widely as a degreasing solvent in developing countries. Typically, patients present with the cutaneous eruptions from 2 weeks to 2 months after occupational exposure. In the evaluation of some of these cases, environmental levels, urinary trichloroethylene concentrations, as well as airborne exposure concentrations were found to be higher than the standard threshold limits.

Idiopathic cases

It is being increasingly recognized that a significant proportion of SJS/TEN are not drug related. From 15% to 25% of cases of SJS/TEN had no prior drug history or occurred in circumstances in which the drug causality was deemed to be unlikely.20 In Singapore, about 10% of SJS/TEN cases were not drug related. In a series of 106 patients, there were three cases attributed to infections with mycoplasma, three cases were associated with systemic lupus erythematosus, and five cases had no drug trigger.19 Similar proportions of non-drug-induced cases were also reported in the Philippines (3/31).14

Pharmacogenetic epidemiology of SJS/TEN

Genetic susceptibility for SJS/TEN has been proposed. It has been clarified that such genetic risks are specific for the type of reaction as well as for the drug and ethnicity. The pharmacogenetic risks of SJS/TEN are best demonstrated in the models of HLA-B*1502 and HLA-B*5801 for CBZ and allopurinol respectively.26,27

<table>
<thead>
<tr>
<th>Associated drug</th>
<th>Singapore N = 159</th>
<th>Malaysia N = 162</th>
<th>Philippines N = 28</th>
<th>Thailand N = 60</th>
<th>Total N = 409</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carbamazepine</td>
<td>29 (29)</td>
<td>34 (21)</td>
<td>4 (14)</td>
<td>4 (7)</td>
<td>71 (17)</td>
</tr>
<tr>
<td>Allopurinol</td>
<td>23 (14)</td>
<td>33 (20)</td>
<td>6 (21)</td>
<td>1 (7)</td>
<td>63 (15)</td>
</tr>
<tr>
<td>Infective sulfonamide</td>
<td>11 (7)</td>
<td>28 (17)</td>
<td>2 (7)</td>
<td>9 (15)</td>
<td>50 (12)</td>
</tr>
<tr>
<td>Phenytoin</td>
<td>14 (9)</td>
<td>13 (8)</td>
<td>5 (18)</td>
<td>4 (7)</td>
<td>36 (9)</td>
</tr>
<tr>
<td>NSAIDs</td>
<td>14 (9)</td>
<td>10 (7)</td>
<td>3 (11)</td>
<td>4 (7)</td>
<td>31 (8)</td>
</tr>
<tr>
<td>Lamotrigine</td>
<td>2 (1)</td>
<td>7 (4)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>9 (2)</td>
</tr>
<tr>
<td>Phenobarbital</td>
<td>2 (1)</td>
<td>0 (0)</td>
<td>3 (11)</td>
<td>1 (2)</td>
<td>6 (1)</td>
</tr>
<tr>
<td>Penicillins</td>
<td>19 (12)</td>
<td>14 (9)</td>
<td>1 (4)</td>
<td>19 (32)</td>
<td>53 (13)</td>
</tr>
<tr>
<td>Other antibiotics</td>
<td>16 (10)</td>
<td>3 (2)</td>
<td>2 (7)</td>
<td>12 (20)</td>
<td>33 (8)</td>
</tr>
<tr>
<td>Others</td>
<td>17 (11)</td>
<td>16 (10)</td>
<td>1 (4)</td>
<td>6 (10)</td>
<td>40 (10)</td>
</tr>
<tr>
<td>Traditional</td>
<td>12 (8)</td>
<td>4 (2)</td>
<td>1 (4)</td>
<td>0 (0)</td>
<td>17 (4)</td>
</tr>
</tbody>
</table>

Data are presented as n (%).

NSAIDs = nonsteroidal anti-inflammatory drugs.
Table 2  Association of HLA-B*1502 and carbamazepine (CBZ) Stevens–Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN).\(^a\)

<table>
<thead>
<tr>
<th>Country</th>
<th>Percentage of SJS/TEN cases attributed to CBZ (%)</th>
<th>HLA-B*1502 population allele frequency (%)</th>
<th>Incidence of HLA-B*1502 in CBZ induced SJS/TEN</th>
</tr>
</thead>
<tbody>
<tr>
<td>Europe(^{20,32,34,40})</td>
<td>4(^{–})8</td>
<td>&lt;0.1 (Germany), 0/13 (Caucasians), 4/4 (Asians in Europe)</td>
<td></td>
</tr>
<tr>
<td>Taiwan(^{26,31,41})</td>
<td>25(^{–})33</td>
<td>Han Chinese: 8.6 41/41 (Han Chinese)</td>
<td></td>
</tr>
<tr>
<td>Malaysia(^{1,42})</td>
<td>24</td>
<td>Malaysian 12/16 (Malays) 8.3</td>
<td></td>
</tr>
<tr>
<td>Philippines(^{14})</td>
<td>13</td>
<td>Filipinos: 22 NA</td>
<td></td>
</tr>
<tr>
<td>Singapore(^{15,19,43})</td>
<td>14(^{–})36</td>
<td>Singapore NA 11.6</td>
<td></td>
</tr>
<tr>
<td>Thailand(^{4,28,29,44})</td>
<td>7</td>
<td>Thais: 8.5 37/42 (Thai)</td>
<td></td>
</tr>
</tbody>
</table>

\(^a\) Allele frequencies derived from references and www.allelefrequency.net.

Table 3  Association of HLA-B*5801 and allopurinol Stevens–Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN).\(^a\)

<table>
<thead>
<tr>
<th>Country</th>
<th>Percentage of SJS/TEN cases attributed to allopurinol (%)</th>
<th>HLA-B*5801 population allele frequency (%)</th>
<th>Incidence of HLA-B*5801 in allopurinol SJS/TEN</th>
</tr>
</thead>
<tbody>
<tr>
<td>Europe(^{20,32,40})</td>
<td>14(^{–})17</td>
<td>1(^{–})6</td>
<td>19/31</td>
</tr>
<tr>
<td>Taiwan(^{27})</td>
<td>17</td>
<td>Han Chinese: 11 21/21</td>
<td></td>
</tr>
<tr>
<td>Malaysia(^{42})</td>
<td>19(^{–})21</td>
<td>Malaysian 6(−)14</td>
<td></td>
</tr>
<tr>
<td>Philippines(^{14})</td>
<td>19</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>Singapore(^{15,19,43})</td>
<td>7(^{–})15</td>
<td>Chinese: 6(−)11</td>
<td></td>
</tr>
<tr>
<td>Malaya(^{1,3})</td>
<td>3(^{–})5</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>Thailand(^{16,33})</td>
<td>2</td>
<td>Thais: 6(−)8 27/27</td>
<td></td>
</tr>
</tbody>
</table>

\(^a\) Allele frequencies derived from references and www.allelefrequency.net.

CBZ

Since the initial study by Chung et al.\(^{26}\), which showed the strong association between HLA-B*1502 and SJS/TEN in Han Chinese in Taiwan, these results have been replicated in other Asian countries including those within SE Asia such as Thailand,\(^{28,29}\) Malaysia,\(^{30}\) and Singapore (submitted for publication). In the original and follow-up studies on Han Chinese in Taiwan, the odds ratio were 2504 [95% confidence interval (CI) 126\(–\)49,522] and 1357 [95% CI 193\(–\)8383], respectively.\(^{20,31}\) In the other SE Asian populations, odds ratio were 16.2 (95% CI 4.6\(–\)62.0) for Malays in Malaysia and 54.76 for Thais in Thailand (95% CI 14.6\(–\)205.1). The association in Caucasian populations is more tenuous. Lonjou et al.\(^{32}\) evaluated 12/16 (Malays) patients carrying the HLA-B*1502 allele and all had Asian ancestry. In Asian populations, the allele frequency of HLA-B*1502 is much higher compared to Caucasian populations (Table 2). This variation in alleleic frequency may, in part, explain the variation in incidence of carbamazepine induced SJS/TEN in SE Asia and Taiwan compared to other populations.

Allopurinol

The link between HLA-B*5801 and allopurinol SCAR was first reported by Hung et al.\(^{17}\) who demonstrated the presence of the allele in 100% (51/51) of patients who developed allopurinol SCAR but only in 15% (20/135) of controls. Similar findings have been seen in Thai populations where 100% (27/27) of patients with allopurinol SCAR carried the HLA-B*5801 allele whereas only 13% (7/54) of the controls carried the allele.\(^{13}\) A meta-analysis of nine studies that analyzed associations studies of HLA-B*5801 and SCAR (four studies using case-matched controls and five studies were population controls) showed an odds ratio of 96.6 (95% CI 24.5\(–\)381) in matched controls or 79.3 (95% CI 41.5\(–\)151.4) in population controls. Subgroup analysis did not show significant differences between Asian and non-Asian populations. Although there are ethnic variations in the frequency of HLA-B*5801, it is significantly less compared to that of HLA-B*1502. The allele frequencies are summarized in Table 3.

Prevention of SJS/TEN within SE Asia

Prescription habits/indications

Primary prevention of SJS/TEN involves limiting exposure to a high-risk drug through correct prescription indications and the use of safer alternatives. The top three common classes of drugs in SE Asia [CBZ and PHT (26%), allopurinol (15%), sulfonamide antibiotics (12%) are prone to such practice lapses. In SE Asia, allopurinol is often prescribed for asymptomatic hyperuricemia and nonspecific joint pains.\(^{34,35}\) Similarly, phenytoin is often used as perioperative seizure prophylaxis although evidence for its efficacy is lacking\(^{36}\) and co-trimoxazole is used for the treatment of acne and folliculitis although safer and effective alternatives are available.

Screening prior to initiation of high-risk drugs

Screening and personalized drug therapy is the goal of pharmacogenetics research. However, prior to when such tests are widely adopted, considerations such as the strength of pharmacogenetic association, the usefulness in therapeutic decision-making (i.e., the presence of alternatives), the medical need, and cost-effectiveness needs to be addressed. The usefulness of HLA screening in preventing morbidity has been validated in the case of HLA-B*1502 and CBZ SJS/TEN in Taiwan.\(^{37}\) Since then, screening prior to initiation of CBZ has also been found to be cost-effective in Taiwan, Malaysia, and Singapore\(^{28,30,38}\) where the prevalence of the HLA-B*1502 is high. With these initiatives in place, it is expected that the incidence of CBZ-induced SJS/TEN in this region will be lower in the future.

Conclusion

Prospective epidemiological studies are required to document the incidence and drug causality of SJS/TEN in Asian populations. The list of high-risk drugs appears similar in Asia and Europe. Although variations in the incidence of SJS/TEN due to specific drugs may be influenced by both prescription practices and the incidence of the underlying medical condition treated, it is likely that ethnic pharmacogenetic differences play a major role. The use of screening prior to initiation is a promising step to further reduce the mortality and morbidity of such reactions.

Acknowledgments

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References


