

Lamotrigine-induced Stevens-Johnson syndrome and toxic epidermal necrolysis in Singapore: A case series

Dear Editor,

With the advancements in pharmacogenetics, potential genetic associations with severe cutaneous adverse drug reactions (SCAR)—which include Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN)—have been proposed. Lamotrigine is one of the 2 anticonvulsants found to be highly associated with SJS/TEN from the 2008 EuroSCAR study. Several studies worldwide have looked at the association of specific human leukocyte antigen (HLA) alleles with lamotrigine-induced SCAR in patients from different geographical and ethnic origins.

In our study, data from patients at 2 tertiary hospitals in Singapore—Singapore General Hospital and National University Hospital—which are part of the ongoing pharmacogenetics study of adverse drug reactions (ADR) of serious skin rash, in collaboration with the Health Sciences Authority (HSA) were retrospectively analysed. A total of 6 patients with a diagnosis of lamotrigine-induced SCAR from January 2003 to September 2018 were recruited. Recruitment was based on physician identification of eligible patients, and written informed consent for blood collection for HLA testing and for medical records access.

Clinical assessments and treatment were conducted by specialist dermatologists correlating the clinical presentation and morphology with temporal drug history, and histology specimens if performed. The percentage of body-surface-area involvement was used to differentiate between SJS (<10%), SJS/TEN overlap (10–30%) and TEN (>30%). Eligibility and identification of the causative drug was made based on “certain” or “probable” causality as per the World Health Organization Uppsala Monitoring Centre (WHO-UMC) criteria and Algorithm for Assessment of Drug Causality (ALDEN) scoring.¹ Patients with “possible” causality were excluded.

HLA genotyping was performed by the Singapore Immunology Network, according to verified methods by Pozzi et al.² Data obtained by sequencing were interpreted by Sequencing Analysis Software (Applied Biosystems, Waltham, US) and checked against a library of HLA sequences and alleles according to the Immunogenetics (IMGT)/HLA Database.³

All of the recruited patients with lamotrigine-induced SCAR had SJS (83%) or TEN (17%). None presented with drug reaction with eosinophilia and systemic symptoms (DRESS) or acute generalised exanthematous pustulosis. None developed significant liver or systemic abnormalities (Table 1). Four of the 6 patients were female. Lamotrigine was determined as the probable single causative agent, with latency of 11–31 days (mean 2.8 weeks), and mean ALDEN score was 4. Three patients had skin biopsies performed, which were consistent with the diagnosis of SJS/TEN, with necrolytic keratinocytes and epidermal detachment. The mean severity-of-illness Score for TEN (SCORTEN) was 1.9 (range 1–3).

Half of the patients (50%) were prescribed lamotrigine for epilepsy, while other medical indications included bipolar disorder (33%) and depression (17%). Lamotrigine was most commonly prescribed at a dose of 25mg daily. All reported the use of concomitant drugs, with valproate being administered concurrently in 50%; and fluoxetine and tranexamic acid in 17%, which were stopped as they were non-essential. ALDEN scoring was performed to help identify the causative drug. Only 1 patient (17%) had reported prior drug allergy to another drug (levofloxacin).

All of the patients were treated with topical steroids such as 0.1% betamethasone valerate or mometasone furoate cream. Two patients (33%) required systemic ciclosporin that was started at 4mg/kg/day and stopped on resolution. None was treated with intravenous human normal immunoglobulin or systemic corticosteroids. All of the patients recovered, with no systemic complications on follow-up. All developed varying degrees of post-inflammatory hyperpigmentation over the previous sites of dermatosis. One patient had persistent oral erosions for 1 month, which resolved after topical triamcinolone application. Beau’s lines were noted on 1 patient’s nails 3 months later. None developed mucocutaneous strictures or vision abnormalities.

There are few studies on lamotrigine-induced SCAR in Southeast Asia. Wang et al. previously proposed risk factors for lamotrigine-induced SCAR as being rapid drug titration, concurrent valproate administration, prior history of anticonvulsant-associated rash, female, and

Table 1. Demographics of patients with lamotrigine-induced SJS or TEN

No. of patients	N=6 No. (%)
Sex	
Female	4 (67)
Male	2 (33)
Ethnicity	
Chinese	2 (33)
Malay	2 (33)
Indian	1 (17)
Eurasian	1 (17)
Age, years, mean±SD (range)	36±13 (20–57)
History of cutaneous adverse reaction to drugs	1 (17)
Mean dosage, mg, mean±SD (range)	27.1±12.3 (12.5–50)
Indication for lamotrigine	
Epilepsy	3 (50)
Bipolar	2 (33)
Depression	1 (17)
Temporal lapse in weeks from start of drug to onset of reaction, mean±SD (range)	2.83±1.17 (2–4)
Concurrent valproate administration	3 (50)
Clinical features	
SJS	5 (83)
TEN	1 (17%)
BSA affected in %, mean±SD (range)	16±20 (8–58)
Treatment	
Topical steroids	6 (100)
Ciclosporin	2 (33)
Intravenous immunoglobulin	0 (0)
Clinical outcome	
Death	0 (0)
Recovery	6 (10)
HLA genotype	
<i>HLA-A*3303</i>	2 (33)
<i>HLA-A*2402</i>	2 (33)
<i>HLA-DRB1*1202</i>	3 (50)

SD: standard deviation; SJS: Stevens-Johnson syndrome; TEN: toxic epidermal necrolysis

age less than 13 years.⁴ Our study has revealed supporting data, whereby majority of patients were female (83%), and half were taking valproate concurrently. As previous reports of lamotrigine-induced SCAR worldwide have been seen in high dosages of more than 100mg/day, some advocate the

use of low dose initiation and slow drug escalation.^{4,5} All of our patients developed SCAR despite being on low doses of lamotrigine with an average of 25mg/day. In future studies, we hope to look at the impact and value of low dosages of anti-epileptics in an Asian context.

Genetic factors are recognised as major risk factors in the development and predisposition of SCARs, with distinct HLA alleles linked with different populations; and the identification of associated alleles can have great utility in the management of SCARs. In Singapore, there are 3 major ethnic groups, with Chinese being the majority (75%), followed by Malays (14%) and Indians (9%). Singapore's HSA, in collaboration with several public healthcare institutions, embarked on a programme in 2009 on the analysis of DNA samples from patients who had experienced drug-induced SCARs, and to capture the phenotypic data associated.⁶ The validation of the association of *HLA-B*1502* allele with carbamazepine-induced SCAR led to the Ministry of Health's implementation and subsidy of *HLA-B*1502* testing in 2013 as the standard-of-care prior to the initiation of carbamazepine, which contributed to a reduction in carbamazepine-induced SJS/TEN in Singapore by 92%.⁷

In our case series (Table 1), there was no specific HLA allele that was demonstrated to be carried by the majority of patients (defined as greater than 50%). Half of the patients were found to carry *HLA-DRB1*1202*. Two patients of Chinese ethnicity were found to carry *HLA-A*2402*, while another one-third had *HLA-A*3303*.

In a 2018 meta-analysis, Deng et al. proposed that *HLA-B*1502* appears to be the risk allele for lamotrigine-induced SJS/TEN in the Asian population (pooled odds ratio [OR] 2.4, 95% confidence interval [CI] 1.20–4.78, $P=0.01$), while *HLA-A*2402* is statistically associated with a susceptibility to either SJS/TEN or maculopapular exanthems (MPE) from lamotrigine⁸ (Table 2). A systematic review of 5 studies with drug-tolerant and population controls found a statistically significant association between the *HLA-A*2402* allele and lamotrigine-induced cutaneous-ADR (cADR) (OR 1.94, 95% CI 1.06–3.54, $P=0.03$).⁹ However, both meta-analyses defined cADRs as inclusive of MPEs, and not solely SCARs. It is noteworthy that only 1 patient in our case series had *HLA-B*1502* (data not shown), and 2 patients had *HLA-A*2402*.

While we did not identify a single major HLA-related genetic risk factor for lamotrigine-induced SCAR, this

is preliminary data and can help guide further larger-scale studies with higher statistical power, and with comparison between drug-tolerant control groups in our Singapore population.

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Table 2. Comparison of observations of lamotrigine-related SCARs from Asia

Author	Country/ Territory	No.	Reported HLA allele(s)
An et al. (2010) ¹⁰	China	3	<i>HLA-B*1502</i> was present in 1 out of 3 (33.3%) cases
Hung et al. (2010) ¹¹	Taiwan	6	<i>HLA-B*1502</i> was present in 2 out of 6 (33.3%) cases
Cheung et al. (2013) ¹²	Hong Kong, China	6	<i>HLA-B*1502</i> was present in 2 out of 6 (33.3%) cases
Kwan et al. (2014) ¹³	Hong Kong, China	6	<i>HLA-B*1502</i> was present in 2 out of 6 (33.3%) cases
Wang et al. (2014) ¹⁴	China	7	<i>HLA-DRB1*1501</i> and <i>HLA-B*1502</i> were present in 4 and 2 out of 7 (57.1% and 28.6%) cases, respectively
Srivastava et al. (2017) ¹⁵	India	3	<i>HLA-B*1502</i> was present in 1 out of 3 (33.3%) cases
Shi et al. (2017) ¹⁶	China	22	<i>HLA-A*2402</i> was present in 10 out of 22 (45.5%) cases
Kim et al. (2017) ¹⁷	South Korea	18	<i>HLA-A*3101</i> was present in 8 out of 18 (44.4%) cases
Koomdee et al. (2018) ¹⁸	Thailand	4	<i>HLA-A*0207</i> and <i>HLA-B*1502</i> were reported in 2 and 1 out of 4 (50% and 25%) cases, respectively

SCAR: severe cutaneous adverse drug reaction

Superscript numbers: refer to REFERENCES

Note: Single studies that defined cutaneous adverse drug reactions as maculopapular exanthems with lamotrigine were not included.

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