Journal of Clinical Neuroscience 18 (2011) 1289–1294

Contents lists available at ScienceDirect

Journal of Clinical Neuroscience

journal homepage: www.elsevier.com/locate/jocn

Review

Pharmacogenetic screening of carbamazepine-induced severe cutaneous allergic reactions ☆

Chaichon Locharernkul [a,d,*], Vorasuk Shotelersuk [b], Nattiya Hirankarn [c]

[a] Department of Medicine, Faculty of Medicine, Chulalongkorn University, Bangkok, Thailand
[b] Department of Pediatrics, Faculty of Medicine, Chulalongkorn University, Bangkok, Thailand
[c] Department of Microbiology, Faculty of Medicine, Chulalongkorn University, Bangkok, Thailand
[d] Chulabhorn Epilepsy Centre (CEC), 54 Moo 4 Vipavadee Rangsit Highway, Laksi, Bangkok 10210, Thailand

ARTICLE INFO

Article history:
Received 23 June 2010
Accepted 12 December 2010

Keywords:
Antiepileptic drug
Clinical practice
Cost-effectiveness
*HLA-B*1502*
Stevens–Johnson syndrome
Toxic epidermal necrolysis

ABSTRACT

Recent studies associated the *HLA-B*1502* allele with carbamazepine (CBZ)-induced Stevens–Johnson syndrome (SJS)/toxic epidermal necrolysis (TEN) in patients from China, Thailand and Malaysia. No association has been found in patients from Europe or Japan. Linkage summary reports from East and South-east Asia predict a highly significant odds ratio (OR) of 84.75 (95% confidence interval [CI] = 42.53–168.91; $p = 8.96 \times 10[-15]$) with sensitivity and negative predictive values of 92% and 98%, respectively. The higher prevalence of *HLA-B*1502* allele among certain Asian populations (10–15%) compared to Caucasians (1–2%) may explain a 10-fold to 25-fold higher incidence of CBZ-SJS/TEN in patients from Asia. Screening for *HLA-B*1502* before using CBZ can prevent SJS/TEN in certain populations, but screening may be less beneficial in populations with low *HLA-B*1502* allele frequency and in patients exposed to CBZ for more than 2 months. A retrospective study demonstrated that the costs of *HLA-B*1502* screening were less than those of SJS treatment. This article reviews possible benefits and concerns of *HLA-B*1502* screening in clinical practice.

© 2011 Published by Elsevier Ltd.

1. Introduction

Therapeutic effects and adverse drug reactions vary from person to person leading to occasional, unpredictable clinical responses. Genetic differences among individuals mainly underlie this phenomenon. Pharmacogenetic awareness helps enhance clinical practice by predicting patients who will show good therapeutic response or suffer potential adverse reactions, and leads to the reality of personalized medicine, or more precisely worded "subgroup" medicine. This article reviews the recently discovered associations between a major histocompatibility complex (MHC) class I allele, *HLA-B*1502*, and severe cutaneous allergic reactions caused by antiepileptic drugs (AED), focusing on carbamazepine (CBZ), including an explanation of the findings, and applications of genetic screening in clinical practice.

Stevens–Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) are among the most severe forms of cutaneous allergic reactions. The clinical manifestations include painful mucosal erosions and wide areas of bullous eruptions resulting from epidermal necrolysis. The extent of skin detachment distinguishes SJS from TEN, corresponding to vesicular eruptions over less than 10% of the body surface and greater than 30%, respectively.[1] SJS/TEN overlap is intermediate. SJS has mortality rate of between 5% and 15% whereas the mortality rate for TEN can be as high as 35%.[2] Corneal scars and visual loss have been reported as disabling permanent sequelae.[3]

SJS/TEN requires emergency treatment, although in a minority of patients, SJS/TEN may resolve spontaneously. Early recognition and immediate withdrawal of all possible causative drugs is the mainstay of treatment, but admission to an ICU or burn unit may be necessary.[4] Supportive care is crucial. Glucocorticoids have not been proven useful in SJS/TEN.[5] They may be beneficial in the early stage of SJS/TEN but may increase the risk of infection, prolonged wound healing,[6] or even increase mortality,[7] if bullous eruption or mucosal erosion is fully developed. The cost of SJS/TEN treatment is usually high due to prolonged hospitalization, possible subsequent visual disabilities, and psychosocial sequelae.

In contrast, a non-bullous maculopapular eruption (MPE) is usually mild and self-limiting upon termination of the offending drugs.[8] However, a severe MPE syndrome, or drug rash with eosinophilia and systemic symptoms (DRESS) can have a mortality rate of 10%[9] and requires treatment with systemic steroids.[10,11]

Among AED reported to cause SJS/TEN are those containing aromatic rings: phenobarbital (PB), phenytoin (PHT), carbamazepine

☆ This study was supported in part by the Light for Life Foundation for Epilepsy (LFE), Thailand.

* Corresponding author. Tel.: +66 2576 6838; fax: +66 2576 6870.
E-mail address: drchaichon@yahoo.com (C. Locharernkul).

0967-5868/$ - see front matter © 2011 Published by Elsevier Ltd.
doi:10.1016/j.jocn.2010.12.054

(CBZ),[12,13] lamotrigine (LTG),[14,15] oxcarbazepine (OXC)[16] and zonisamide (ZNS).[17] There is no clear evidence that valproic acid (VPA) is a culprit drug for SJS/TEN since reports have been confounded by the concomitant use of other causal drugs.[18,19] These AED are also used in conditions other than epilepsy such as neuropathic pain, mood disorders and paroxysmal choreoathetosis. Patients exposed to such AED under these non-epileptic conditions can also be at risk of developing SJS/TEN.

2. The Associations between the *HLA-B*1502* allele and induced SJS/TEN

A strong association between *HLA-B*1502*, a human leukocyte antigen belonging to MHC class I, and CBZ-induced SJS/TEN was first reported in Han Chinese patients residing in Taiwan.[20] All 44 patients with CBZ-induced SJS/TEN carried *HLA-B*1502* whereas 3% of CBZ-tolerant ($n = 101$) and 8.6% healthy controls ($n = 93$) tested positive. This gave an odds ratio (OR) of 2504 (95% confidence interval (CI) of 126–49,522), the strongest so far described between an human leukocyte antigen (HLA) and a disorder. No other HLA genotypes were associated with CBZ–SJS/TEN, except for some ancestral haplotypes which were conserved alleles coupled at closely linked loci (*CW*0801*, *A*1101* and *DRB1*1202*).

This association was later confirmed in their extended study involving 60 patients with CBZ–SJS/TEN among 91 Chinese or Chinese descendants from Taiwan ($n = 88$), Hong Kong ($n = 2$) and the USA ($n = 1$).[21] Also included were 13 patients with hypersensitivity syndrome (HSS), 18 MPE, 144 CBZ-tolerant patients and 93 healthy controls. *HLA-B*1502* was present in 98.3% of patients with CBZ–SJS/TEN ($n = 60$) in contrast to only 4.2% of tolerant control patients ($n = 144$). The association showed high statistical significance with an OR of 1357 (95% CI = 193–8838), while the association was not observed in the patients with MPE or HSS. No other MHC gene or single nucleotide polymorphism was found associated with CBZ–SJS/TEN. Only *CW*0801* and *MICA*019* alleles showed strong linkage disequilibrium with *HLA-B*1502*.

The same genetic susceptibility was shown in another study involving six Han Chinese patients with AED-induced severe cutaneous reactions (four to CBZ, one to LTG and one to PHT) in Hong Kong.[15] *HLA-B*1502* was present in all SJS/TEN patients whereas only 14.5% of 48 tolerant controls tested positive, giving an OR of 71.9 (95% CI = 3.7–1415.8). Two patients with HSS were *HLA-B*1502* negative. No differences in *HLA-B*1502* allele frequencies were found between the 16 patients with MPE (12.5%) and the controls (14.5%).

A study in Malaysia presented 21 patients with CBZ–SJS/TEN in a mixed population (16 from Malaysia, three from China and two from India). *HLA-B*1502* was positive in 75% (12 out of 16 Malaysian patients) but in only 15.7% (47 out of 300) race-matched healthy controls. The *HLA-B*1502* association was found to be statistically significant with an OR of 16.15 ($p < 0.0001$).[22]

A study conducted in a Bangkok comprehensive epilepsy center, including patients from all regions of Thailand, also found a significant association between *HLA-B*1502* and SJS induced by either CBZ or PHT.[23] All 10 patients with SJS (six with CBZ and four with PHT) carried the *HLA-B*1502* allele. No other *HLA-B* alleles were associated with SJS. When the allele frequency in 50 tolerant control patients (38 tolerant to CBZ and PHT, four tolerant to CBZ, seven tolerant to PHT and one tolerant to VPA) were compared, strong associations were shown between *HLA-B*1502* and CBZ–SJS (OR = 25.5; 95% CI = 2.7–242.6; $p = 0.0005$) and between *HLA-B*1502* and PHT–SJS (OR = 18.5; 95% CI = 1.8–188.4; $p = 0.005$). No significant association was found in 21 patients with CBZ- or PHT-induced MPE (five CBZ-induced, nine PHT-induced and seven combined AED-induced). The ethnicity of 10 patients with SJS/TEN was three pure Thai and seven of mixed origin (three Thai–Chinese, two Thai–Chinese–Peguan [Mon], one Thai–Peguan and one Thai–Vietnamese).

A multicenter study carried out in north-eastern Thailand involving 42 Thai and Thai–Chinese patients also showed strong association between *HLA-B*1502* and CBZ–SJS/TEN.[24] The *HLA-B*1502* allele was positive in 88.1% of 42 patients with CBZ–SJS/TEN but in only 11.9% of 42 tolerant controls, giving an OR of 54.76 (95% CI = 14.62–205.13).

Interestingly, the association between *HLA-B*1502* and CBZ–SJS/TEN was population specific. The allele was not found in eight out of 12 Caucasian patients with CBZ–SJS/TEN (six French and two Germans).[25] However, the remaining four patients who tested positive in this study were of Asian descent (one each from Vietnam, China, Cambodia and Reunion Island). In another study in the United Kingdom involving 99 people of Caucasian descent, which consisted of 20 patients with severe cutaneous reactions (18 with DRESS and two with SJS/TEN) and 36 PTH-tolerant and 43 CBZ-tolerant controls, the *HLA-B*1502* allele was not found to be a genetic marker among all subjects.[26] Only two patients with CBZ–SJS/TEN were included in this study.

In Japan, a multicenter study of 58 patients, which included seven patients with CBZ–SJS/TEN, also reported no association with *HLA-B*1502*.[17] A subsequent study including five patients with CBZ–SJS from Japan found suggestive associations with *HLA-B*1518*, *HLA-B*5901* and *HLA-C*0704* alleles, but not with *HLA-B*1502*.[27]

These findings show that *HLA-B*1502* is a strong genetic marker for CBZ–SJS/TEN with ethnic preponderance in certain Asian populations. In Table 1, in which the current findings of the genetic susceptibility of all reported articles concerning East and South-east Asian populations is summarized, a highly significant OR of 84.75 (95% CI = 42.53–168.91; $p = 8.96 \times 10^{-15}$) with very high sensitivity of 92% and negative predictive value of 98% is predicted in certain Asian people. However, a false positivity of 4.2% to 19% was seen in CBZ-tolerant controls.

Association between *HLA-B*1502* and severe cutaneous allergic reactions induced by other AED have also been reported. PHT–SJS was associated with *HLA-B*1502* in one patient from a Han Chinese series.[15] Statistical significance was first shown in a Thai study.[23] All four patients with PHT–SJS carried the *HLA-B*1502* allele, whereas eight out of 45 PHT-tolerant controls tested positive, giving a significant OR of 18.5.

The association between *HLA-B*1502* and LTG-induced[15] or OXC-induced severe cutaneous reactions[16] was reported in an individual Chinese patient from two separate studies. HLA genotyping performed in patients of European ancestry suffering from LTG-induced severe cutaneous reactions found no association with *HLA-B*1502* but had a marginal association with *HLA-B*5801*, *-Cw*0718* and *-DQB1*0609*, the latter two alleles strongly correlated with *HLA-B*5801*.[28,29] The findings again show ethnic preponderance of genetic susceptibility to AED-induced SJS/TEN.

No association between *HLA-B*1502* and AED-induced HSS or MPE has been shown.[15,21,23] This suggests a possible difference in the genetic–immunologic mechanism between SJS/TEN and HSS/MPE. Non-bullous cutaneous reactions were associated with biomarkers other than *HLA-B*1502*. In Han Chinese, CBZ–MPE/HSS showed genetic linkage to *HLA-A*3101* (OR = 12.17; 95% CI = 3.6–41.2). CBZ–HSS was not linked to the *HLA-B* marker as in CBZ–SJS/TEN, but to motilin gene polymorphisms in the MHC class II terminal region.[21] Protective effects of *HLA-B*0702* against CBZ-induced severe cutaneous reactions was found in a study with Caucasian patients.[26] The findings regarding HSS/MPE biomarkers need replication before conclusions can be drawn.

In summary, the available information demonstrates a strong genetic association between *HLA-B*1502* and CBZ–SJS/TEN in

Table 1
Studies conducted in Asia of the association between carbamazepine (CBZ)-induced Stevens–Johnson syndrome (SJS)/toxic epidermal necrolysis (TEN) and the *HLA-B*1502* allele

Study no./Year[ref]	Patient groups	No.	Ethnicity	*HLAB*1502*	Non-*HLAB*1502*	*p*-Value	OR	95% CI
1/2006[21]	CBZ-SJS/TEN	60	Han Chinese	59	1	1.6×10^{-41}	1357	193.4–8838.3
	CBZ-tolerant controls	144		6	138			
2/2007[15]	CBZ-SJS/TEN	4(6)[†]	Han Chinese	4(6)[†]	0(0)[†]	1.48 × 10–4	71.9	3.7–1415.8
	Controls[‡]	48		7	41			
3/2008[22]	CBZ-SJS	21	Malaysian, Chinese, Indian	17(12)[¶]	4(4)[¶]	<0.0001	16.15[§]	–
	Controls[††]	300		47	253			
4/2008[23]	CBZ-SJS/TEN	6	Thai, mixed Thais	6	0	0.0005	25.5	2.68–242.61
	CBZ-tolerant controls	42		8	34			
5/2010[24]	CBZ-SJS	42	Thai, Thai–Chinese	37	5	2.89×10^{-12}	54.76	14.62–205.13
	CBZ-tolerant controls	42		5	37			
All Asian studies:								
SJS/TEN		133		123	10	8.96×10^{-15}	84.75	42.53–168.91
Controls		576		73	503			

AED = Antiepileptic drugs, CI = confidence interval, LTG = lamotrigine, OR = odds ratio, PB = phenobarbital, PHT = phenytoin, TPM = topiramate, VPA = valproic acid.
[†] Patients with CBZ-SJS/TEN = four, PHT-SJS/TEN = one and LTG-SJS/TEN = one. Numbers in parentheses were used to calculate OR in the article; numbers without parentheses were used in this combined calculation.
[‡] AED-tolerant controls (CBZ, LTG, PB, PHT, TPM, VPA); positivity of *HLA-B*1502* in 16 CBZ-tolerant controls were not mentioned in the article.
[§] Sensitivity = 92%, specificity = 87% (no other details were available in the abstract).
[¶] 21 Patients with CBZ-SJS/TEN: 16 from Malaysia, three from China and two from India; 12 out of 16 patients from Malaysia and all from China and India were positive for *HLA-B*1502*. Numbers in parentheses were used to calculate OR in the article; numbers without parentheses were used in this combined calculation.
[††] Race-matched healthy controls.

patients residing in South-east Asia and Eastern China, as well as a small population of European or American residents with Asian ancestry. The significant association of PHT–SJS/TEN with *HLA-B*1502* was also found in a few Asian patients of which findings need replication in broader populations. The *HLA-B*1502* allele is one of the pharmacogenetic biomarkers that shows clear preponderance to ethnicity in a certain geographic distribution.[25]

3. Current explanations

It is unclear how *HLA-B*1502* is responsible for the phenotype of SJS/TEN induced by CBZ or other AED. The *HLA-B*1502* allele is found in high prevalence among population in the East and South-east Asian regions,[30] being most prevalent (9–10%) in the Han Chinese in China.[31] People in Thailand, Malaysia, Singapore, Philippines and the Khandish Pawra region of India have a prevalence of more than 5%. A high prevalence of 5% is also seen in Asians residing in North America.[32] The *HLA-B*1502* is one of the most common *HLA-B* alleles among Thai,[33] Burmese,[34] Vietnamese[35] and Western Javanese[36] but is rare in Caucasians. In a prior study of European populations, the allele frequency was only 1% to 2%.[37]

If the association between *HLA-B*1502* and AED-induced severe cutaneous allergic reactions has a role in the pathogenesis of SJS/TEN, higher incidences of such complications should be seen in particular Asian subgroups compared to Caucasians. A review of the prevalence of SJS/TEN in the world populations seems to support this hypothesis.

In the US Food and Drug Administration (FDA) post-marketing adverse events reports, the frequencies of SJS/TEN were more than 10 times higher in some Asian people (from Malaysia, Thailand, Taiwan, the Philippines) than those in Caucasians.[38,39] The cumulative estimate report by Novartis, the CBZ manufacturer, between 2000 and 2006, revealed an SJS/TEN incidence of 4.1 to 5.9 per 10,000 patient year exposure in some Asian countries, whereas only 0.2 to 0.9 per 10,000 were reported in European countries and USA.[40] The occurrence of adverse cutaneous drug reactions among new CBZ users was 1–6 per 10,000 in Caucasian patients,[14,41] compared to 17–25 per 10,000 in Thailand and Taiwan.[23,42] This confirms an approximately 3-fold to 25-fold higher frequency in Asian populations than in Caucasians. The presence of the *HLAB*1502* allele in high frequency seems to correlate with the high incidence of CBZ-SJS/TEN among certain Asian populations.[13]

The MHC class I and II molecules expressed on the cell membrane form grooves capable of binding to specific antigenic peptides and present them to specific T cells. Differences in MHC among individuals determine variations in immune reactions specific to different drugs. Activation of helper T-cells with increased expression of *CD25* and *HLA-DR* has been shown to be a mechanism of non-immediate cutaneous reactions from drugs.[43] As evidenced by the experimental finding that specific T-cell clones of patients with CBZ-MPE/HSS may recognize CBZ depending on the presence of HLA class-matched antigen-presenting cells,[44] the interaction of T-cell receptor complex and MHC (TRC-MHC-peptide) may initiate CBZ-specific immune responses in SJS/TEN. CBZ-specific CD4+, CD8+ and CD4+CD8+ T cells has been identified and characterized.[45] Of interest, CBZ rapidly stimulates T cells via a direct interaction with MHC and specific T-cell antigen-specific receptors, without a requirement for antigen processing.[46]

*HLA-B*1502* seems to be involved in SJS/TEN for certain drugs in certain patients. Some *HLA-B*1502*-positive patients who developed SJS from CBZ were tolerant to formerly prescribed aromatic AED such as PB, PHT or LTG.[23] Additionally, the mere presence of *HLA-B*1502* does not seem to be sufficient to cause SJS/TEN from CBZ. About 4% to 19% of CBZ-exposed patients who harbor *HLA-B*1502* do not develop SJS/TEN, making a false positivity of as high as 19%.[17,20,22–24]

Although the presence of *HLA-B*1502* may not entirely explain the mechanism of severe cutaneous allergic reactions associated with a single gene allele at a single locus, evidence suggests it is unlikely that the association resulted from a strong linkage disequilibrium with other genes (for example, *CW*0801* and *MICA*019*).[21,28] Other CBZ-specific immune mediators (for example, tumor necrosis factor-alpha[47] or cytotoxic T-cells[48]) have been demonstrated and could play a part in final keratocyte apoptosis. However, the initial trigger interaction between the drug and genetic susceptibility is unclear. While drug-specific activation of cytokine-producing cytotoxic CD8+ T cells has been demonstrated in abacavir hypersensitivities, of which the antigen recognition is uniquely restricted by *HLA-B*5701*,[49] specific CBZ modified peptides have not been detected among many peptides bound to *HLA-B*1502* in patients with CBZ-SJS/TEN.[48]

The *HLA-B*1502* allele is not only insufficient, but its presence is also not necessary in the causation of SJS/TEN. This is evidenced by

the absence of *HLA-B*1502* in Caucasian and Japanese patients who developed CBZ-SJS/TEN.[17,25] Other *HLA* alleles may also have a role in SJS/TEN across different ethnic groups exposed to different drugs. From the available evidence, the only conclusion that can be drawn is that *HLA-B*1502* is strongly associated with CBZ-SJS/TEN in certain Asian populations. A patient's ethnicity is related to the prevalence of *HLA-B*1502*, the strength of association between the biomarker and AED-SJS/TEN and, as a result, the incidence of SJS/TEN in the population. The mechanisms between ethnicity, genetics, reactions to drugs and phenotypic correlation need to be further elucidated.

4. Applications to clinical practice

After the significant association between *HLA-B*1502* and CBZ-SJS/TEN was documented, the US–FDA announced in the 12/12/2007 FDA Alert[38] that "patients with ancestry in at-risk population should be screened for the *HLA-B*1502* allele prior to starting CBZ" and that "patients who test positive for *HLA-B*1502* should not be treated with CBZ unless the expected benefit clearly outweighs the increased risk of SJS/TEN". They also recommended that the screening information be reflected in updated CBZ labeling.

In another FDA Alert on 11/24/2008,[50] based on subsequent data of the association between *HLA-B*1502* and PHT-SJS/TEN, it was stated that "health care providers should consider avoiding PHT and fosphenytoin as alternatives for CBZ in patients who test positive for *HLA-B*1502*".

Pharmacogenetic screening of *HLA-B*1502* before starting CBZ seems promising to prevent life-threatening allergic reactions. One practical question to be addressed is which groups of patients need to be screened.

Screening *HLA-B*1502* in a population carrying high frequency of this allele is obviously more beneficial than testing in those carrying low allele frequencies. Since evidence suggests a high prevalence of *HLA-B*1502* and high incidences of AED-induced SJS/TEN in South-east Asian countries and China, it is prudent to conduct *HLA-B*1502* screening in people residing in, or migrating from, the following specific geographic regions: South-east and Eastern China, Taiwan, Thailand and Malaysia, where the strong association between SJS/TEN and *HLA-B*1502* has been firmly established. People residing in other Asian countries having high prevalence of *HLA-B*1502*, but with no known association, such as Singapore, Vietnam, Indonesia, the Philippines, some parts of India, as well as people of Asian ancestry living in other continents are also recommended testing.[38] For populations with low *HLA-B*1502* allele frequencies (less than 1%) and without genetic associations found, Japanese or Caucasians, the yield of screening is apparently modest. According to the available data, no possible estimation of the screening advantage can be made in other countries where the prevalence of *HLA-B*1502* and genetic susceptibility are unknown.

Most of the allergic reactions to CBZ develop within the first 2 months after starting the drug.[41] Patients tolerant to CBZ for more than 2 months may be considered having low risk for developing SJS/TEN and do not need to be screened.

In Fig. 1 the possible strategies for screening that will affect the cost-effectiveness of *HLA-B*1502* testing in clinical practice are presented.[51] The worthiness of screening prior to prescribing CBZ depends upon the extra cost of the test in a given population, whether it outweighs the costs of SJS/TEN treatment, expense of alternative safer drugs, subsequent loss and sequelae of the ailment.

At present, a genetic test for *HLA-B*1502* is unavailable in most hospitals around the world, especially in developing countries. The test is based on the polymerase chain reaction (PCR)–DNA amplification technique, requires experienced laboratory staff and takes several hours for the results. Although the causative drug may be discontinued, bullous eruptions can quickly develop after early presentation of rash symptoms and it is therefore safer to test for the allele and know the result before starting CBZ treatment. Screening may be inconvenient in an outpatient epilepsy setting by delaying CBZ initiation and imposing additional costs. Faster and cheaper approaches in *HLA* genotyping have been developed recently, which could make it suitable for an outpatient setting. A 1-hour loop-mediated isothermal amplification procedure-based DNA amplification technique has been developed in Hong Kong to substitute for the time-consuming PCR technique.[52] A 4-hour, PCR-based test kit has been developed and marketed in Taiwan.[53] Application of these tests in different ethnic groups needs careful interpretation due to the presence of population-specific *HLA-B* alleles which can possibly result in false positivity.

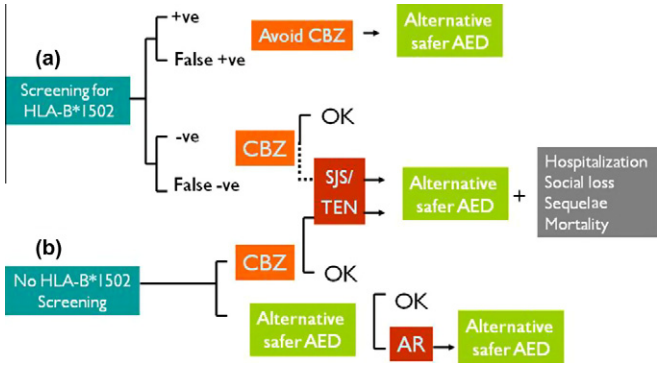

Fig. 1. Schematic of strategies in evaluating cost effectiveness of blood screening for the *HLA-B*1502* allele prior to prescribing carbamazepine (CBZ) in an outpatient epilepsy setting showing that (a) screening for *HLA-B*1502* can prevent the possible Steven–Johnson syndrome/toxic epidermal necrolysis (SJS/TEN) by avoiding CBZ in test-positive individuals, but may be misleading in 5% to 19% of patients who are false positive; in contrast, in most patients who are *HLA-B*1502* negative, CBZ can be used rather safely since the negative predictive value is very high (98%); and (b) without *HLA-B*1502* screening, there is low risk of developing SJS/TEN that may increase medical costs, social loss as well as morbidity and mortality, but without *HLA-B*1502* screening, alternative safer antiepileptic drug (AED) can be used. This strategy may cost more, or still carries a risk of hypersensitivity or adverse reactions (AR), depending on which AED is used. (This figure is available in colour at www.sciencedirect.com.)

In Thailand, *HLA-B* genotyping utilizing PCR techniques costs approximately US$80–95 (3,000 Baht) per test. Testing can be cheaper when blood is tested specifically for the *HLA-B*1502* allele rather than the whole *HLA* or *HLA-B* genomes. A retrospective cost-effectiveness analysis of the *HLA-B*1502* screening done in Thailand showed that the costs of screening per case using the PCR-based *HLA-B* genotyping kit exceeded those of SJS/TEN treatment. Screening costs less than SJS treatment when the specific test for *HLA-B*1502* is used (US$27–32 or 1,000 Baht per test) (Fig. 2). However, the cost-effectiveness of *HLA-B*1502* screening in clinical practice among different ethnic groups should be systematically evaluated.

The expense of alternative AED for CBZ also affects the cost-benefit of the screening. PHT, LTG, OXC and ZNS have induced SJS/TEN so they are not suitable to be used as alternative drugs. Fosphenytoin should also be avoided in *HLA-B*1502*-positive patients.[50] In Thailand, the cost price per tablet of other novel AED such as gabapentin, pregabalin, levetiracetam or topiramate is approximately 2 to 5 times higher than the cost price of CBZ and 5 to 10 times higher than that of PHT, while the cost of VPA, a broad-spectrum first-line AED, is comparable to CBZ but slightly higher than PHT. The use of an alternative drug in test-positive patients seems to be cheaper than the costs of SJS/TEN treatment without screening but this speculation needs to be confirmed. Using a safer AED without performing the

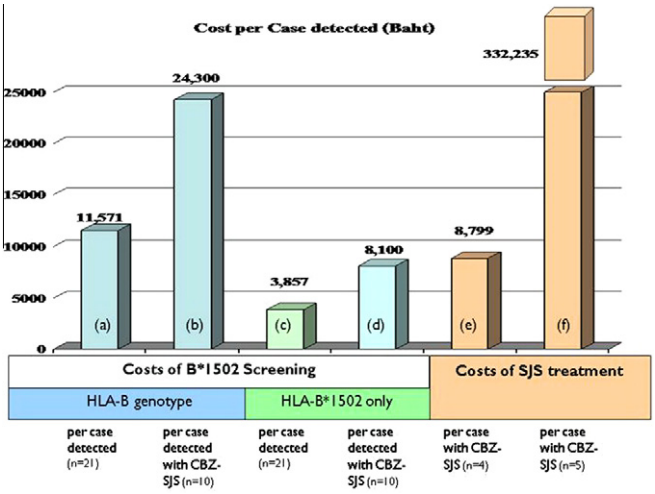

Fig. 2. Cost-effectiveness study of *HLA-B*1502* screening to prevent Steven–Johnson syndrome/toxic epidermal necrolysis (SJS/TEN) from carbamazepine showing: (a) and (b) compared to (e) that the costs of *HLA-B*1502* screening per case detected will exceed those of SJS treatment when a polymerase chain reaction-based *HLA-B* genotyping kit was used; whereas (c) and (d) compared to (e), screening costs will be less than SJS treatment if a *HLA-B*1502*-specific test is used. (f) The cost of SJS treatment per case, which included one patient who had an unusually prolonged hospitalization. (This figure is available in colour at www.sciencedirect.com.)

*HLA-B*1502* screening is another line of practice challenging cost-effectiveness evaluation. Nonetheless, a drug may be considered "safe" only because its adverse effect has not yet been revealed. A recent study demonstrated that use of VPA in early pregnancy could result in impaired cognitive function in the child, a serious adverse effect.[54]

Screening of genetic susceptibility can raise some ethical issues. While a person at high-risk of developing SJS/TEN will benefit, this incurs an additional cost. It is uncertain in most countries whether the policy of health care providers, insurers or employers will financially support the expenses of this new test. Another risk to be considered is the possibility of discrimination on genetic grounds once personal genetic information has been revealed by a blood test.

There are still some practical problems to be solved. How can *HLA-B*1502* be used to prevent SJS/TEN induced by PHT or other aromatic AED? What is the association between *HLA-B*1502* and SJS/TEN in other ethnic groups? Are there other undiscovered strong genetic predictors for AED-induced severe cutaneous allergic reactions? How can ethnicity be reliably identified? How can cross-cultural marriage or migration influence these genotypic distributions? Large-scale study in various ethnic groups and prospective studies of the cost-effectiveness of this biomarker screening are needed to answer the above questions.

5. Conclusions

Application of *HLA-B*1502* screening to prevent CBZ-induced severe allergic reactions is a good example of potential pharmacogenetic applications in medicine. While the significance of these findings in modifying our clinical practice is to be validated, they offers us promise of how our expanding knowledge of pharmacogenetics can benefit certain individuals.

Acknowledgement

This article is supported in part by the Light for Life Foundation for Epilepsy (LFE), Thailand. We thank the Research Unit, Faculty of Medicine, Chulalongkorn University for editing the manuscript, Dr. Thanawath Ratanadilok Na Phuket for assisting with English translation and Ms. Waraphorn Krongthong for her statistical analysis.

References

1. Roujeau JC. The spectrum of Stevens–Johnson syndrome and toxic epidermal necrolysis: a clinical classification. *J Invest Dermatol* 1994;**102**:28S–30S.
2. Ghislain PD, Roujeau JC. Treatment of severe drug reactions: Stevens–Johnson syndrome, toxic epidermal necrolysis and hypersensitivity syndrome. *Dermatol Online J* 2002;**8**:5.
3. Power WJ, Ghoraishi M, Merayo-Lloves J, et al. Analysis of the acute ophthalmic manifestations of the erythema multiforme/Stevens–Johnson syndrome/toxic epidermal necrolysis disease spectrum. *Ophthalmology* 1995;**102**:1669–76.
4. McGee T, Munster A. Toxic epidermal necrolysis syndrome: mortality rate reduced with early referral to regional burn center. *Plast Reconstr Surg* 1998;**102**:1018–22.
5. Schneck J, Fagot JP, Sekula P, et al. Effects of treatments on the mortality of Stevens–Johnson syndrome and toxic epidermal necrolysis: a retrospective study on patients included in the prospective EuroSCAR Study. *J Am Acad Dermatol* 2008;**58**:33–40.
6. Revuz JE, Roujeau JC. Advances in toxic epidermal necrolysis. *Semin Cutan Med Surg* 1996;**15**:258–66.
7. Kelemen JJ, Cioffii WG, McManus WF, et al. Burn center care for patients with toxic epidermal necrolysis. *J Am Coll Surg* 1995;**180**:273–8.
8. Mayorga C, Torres MJ, Fernandez J, et al. Cutaneous symptoms in drug allergy: what have we learnt? *Curr Opin Allergy Clin Immunol* 2009;**9**:431–6.
9. Bocquet H, Bagot M, Roujeau JC. Drug-induced pseudolymphoma and drug hypersensitivity syndrome (Drug Rash with Eosinophilia and Systemic Symptoms: DRESS). *Semin Cutan Med Surg* 1996;**15**:250–7.
10. Autret-Leca E, Norbert K, Bensouda-Grimaldi L, et al. DRESS syndrome, a drug reaction which remains bad known from paediatricians. *Arch Pediatr* 2007;**14**:1439–41 [French].
11. Ben m'rad M, Leclerc-Mercier S, Blanche P, et al. Drug-induced hypersensitivity syndrome: clinical and biologic disease patterns in 24 patients. *Medicine (Baltimore)* 2009;**88**:131–40.
12. Chan HL, Stern RS, Arndt KA, et al. The incidence of erythema multiforme, Stevens–Johnson syndrome, and toxic epidermal necrolysis. A population-based study with particular reference to reactions caused by drugs among outpatients. *Arch Dermatol* 1990;**126**:43–7.
13. Roujeau JC, Kelly JP, Naldi L, et al. Medication use and the risk of Stevens–Johnson syndrome or toxic epidermal necrolysis. *N Engl J Med* 1995;**333**:1600–7.
14. Mockenhaupt M, Messenheimer J, Tennis P, et al. Risk of Stevens–Johnson syndrome and toxic epidermal necrolysis in new users of antiepileptics. *Neurology* 2005;**64**:1134–8.
15. Man CB, Kwan P, Baum L, et al. Association between HLA-B∗1502 allele and antiepileptic drug-induced cutaneous reactions in Han Chinese. *Epilepsia* 2007;**48**:1015–8.
16. Lin LC, Lai PC, Yang SF, et al. Oxcarbazepine-induced Stevens–Johnson syndrome: a case report. *Kaohsiung J Med Sci* 2009;**25**:82–6.
17. Kaniwa N, Saito Y, Aihara M, et al. HLA-B locus in Japanese patients with anti-epileptics and allopurinol-related Stevens–Johnson syndrome and toxic epidermal necrolysis. *Pharmacogenomics* 2008;**9**:1617–22.
18. Rzany B, Correia O, Kelly JP, et al. Risk of Stevens–Johnson syndrome and toxic epidermal necrolysis during first weeks of antiepileptic therapy: a case-control study. Study Group of the International Case Control Study on Severe Cutaneous Adverse Reactions. *Lancet* 1999;**353**:2190–4.
19. Kocak S, Girisgin SA, Gul M, et al. Stevens–Johnson syndrome due to concomitant use of lamotrigine and valproic acid. *Am J Clin Dermatol* 2007;**8**:107–11.
20. Chung WH, Hung SI, Hong HS, et al. Medical genetics: a marker for Stevens–Johnson syndrome. *Nature* 2004;**428**:486. **102**:28S–30S.
21. Hung SI, Chung WH, Jee SH, et al. Genetic susceptibility to carbamazepine-induced cutaneous adverse drug reactions. *Pharmacogenet Genom* 2006;**16**:297–306.
22. Chang CC, Too CL, Murad S, et al. Association of HLA-B∗1502 with carbamazepine-induced toxic epidermal necrolysis and Stevens–Johnson syndrome in Malaysian population. In Proceedings of the 7th Asian-Oceanian Epilepsy Congress, Xiamen 2008. p. 32 (abstract).
23. Locharernkul C, Loplumlert J, Limotai C, et al. Carbamazepine and phenytoin induced Stevens–Johnson syndrome is associated with HLA-B∗1502 allele in Thai population. *Epilepsia* 2008;**49**:2087–91.
24. Tassaneeyakul W, Tiamkao S, Jantararoungtong T, et al. Association between HLA-B∗1502 and carbamazepine-induced severe cutaneous adverse drug reactions in a Thai population. *Epilepsia* 2010;**51**:926–30.
25. Lonjou C, Thomas L, Borot N, et al. A marker for Stevens–Johnson syndrome: ethnicity matters. *Pharmacogenomics* 2006;**6**:265–8.
26. Alfirevic A, Jorgensen AL, Williamson PR, et al. HLA-B locus in Caucasian patients with carbamazepine hypersensitivity. *Pharmacogenomics* 2006;**7**:813–8.
27. Ikeda H, Takahashi Y, Yamazaki E, et al. HLA Class I markers in Japanese patients with carbamazepine-induced cutaneous adverse reactions. *Epilepsia* 2010;**51**:297–300.

28. Lonjou C, Borot N, Sekula P, et al. A European study of HLA-B in Stevens–Johnson syndrome and toxic epidermal necrolysis related to five high-risk drugs. *Pharmacogenet Genom* 2008;**18**:99–107.
29. Kazeem GR, Cox C, Aponte J, et al. High-resolution HLA genotyping and severe cutaneous adverse reactions in lamotrigine-treated patients. *Pharmacogenet Genom* 2009;**19**:661–5.
30. Solberg OD, Mack SJ, Lancaster AK, et al. Balancing selection and heterogeneity across the classical human leukocyte antigen loci: a meta-analytic review of 497 population studies. *Hum Immunol* 2008;**69**:443–64.
31. Yao Y, Shi L, Shi L, et al. Distribution of HLA-A, -B, -Cw, and -DRB1 alleles and haplotypes in an isolated Han population in Southwest China. *Tissue Antigens* 2009;**73**:561–8.
32. Middleton D. International histocompatibility working group. Available at URL: http://www.allelefrequencies.net and www.ihwg.org [search 26 Jan 2009].
33. Romphruk A, Phongaen K, Chotechai J, et al. HLA-B∗15 subtypes in the population of north-eastern Thailand. *Eur J Immunogenet* 2003;**30**:153–8.
34. Kongmaroeng C, Romphruk A, Ruangwerayut R, et al. HLA-B∗15 subtypes in Burmese population by sequence-based typing. *Tissue Antigens* 2009;**74**:164–7.
35. Hoa BK, Hang NT, Kashiwase K, et al. HLA-A, -B, -C, -DRB1 and -DQB1 alleles and haplotypes in the Kinh population in Vietnam. *Tissue Antigens* 2008;**71**:127–34.
36. Yuliwulandari R, Kashiwase K, Nakajima H, et al. Polymorphisms of HLA genes in Western Javanese (Indonesia): close affinities to Southeast Asian populations. *Tissue Antigens* 2009;**73**:46–53.
37. Geer L, Terasaki PI, Gjertson DJ. HLA frequency. In: Gjertson DW, Terasaki PI, editors. HLA 1998. Lenexa: American Society for Histocompatibility and Immunogenetics 1998. p. 327–63.
38. FDA Alert 12/12/2007. Dangerous or even fatal skin reactions – Carbamazepine (marketed as Carbatrol, Equetro, Tegretol and generics) – Healthcare Professional Sheet text version. Available at URL: http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm124718.htm [search 26 Jan 2009].
39. Lim KS, Kwan P, Tan CT. Association of HLA-B∗1502 allele and carbamazepine induced severe adverse cutaneous drug reaction among Asians, a review. *Neurol Asia* 2008;**13**:15–21.
40. Farkas R. Clinical Review, Adverse Events of Carbamazepine, 2007. Available at URL: http://www.fda.gov/cder/foi/nda/2007/016608s098,020712s029,021710_ClinRev.pdf [search 26 Jan 2009].
41. Tennis P, Stern RS. Risk of serious cutaneous disorders after initiation of use of phenytoin, carbamazepine, or sodium valproate: a record linkage study. *Neurology* 1997;**49**:542–6.
42. Hung SI, Chung WH, Chen YT. HLA-B genotyping to detect carbamazepine-induced Stevens–Johnson syndrome: implications for personalizing medicine. *Personalized Med* 2005;**2**:225–37.
43. Mayorga C, Blanca M. Nonimmediate allergic reactions induced by drugs: pathogenesis and diagnostic tests Review. *J Investig Allergol Clin Immunol* 2009;**19**:80–90.
44. Naisbitt DJ, Britschgi M, Wong G, et al. Hypersensitivity reactions to carbamazepine: characterization of the specificity, phenotype, and cytokine profile of drug-specific T cell clones. *Mol Pharmacol* 2003;**63**:732–41.
45. Wu Y, Farrell J, Pirmohamed M, et al. Generation and characterization of antigen-specific CD4+, CD8+, and CD4+CD8+ T-cell clones from patients with carbamazepine hypersensitivity. *J Allergy Clin Immunol* 2007;**119**:973–81.
46. Wu Y, Sanderson JP, Farrell J, et al. Activation of T cells by carbamazepine and carbamazepine metabolites. *J Allergy Clin Immunol* 2006;**118**:233–41.
47. Pirmohamed M, Lin K, Chadwick D, et al. TNF alpha promoter region gene polymorphisms in carbamazepine hypersensitive patients. *Neurology* 2001;**56**:890–6.
48. Yang CW, Hung SI, Juo CG, et al. HLA-B∗1502-bound peptides: implications for the pathogenesis of carbamazepine-induced Stevens–Johnson syndrome. *J Allergy Clin Immunol* 2007;**120**:870–7.
49. Chessman D, Kostenko L, Lethborg T, et al. Human leukocyte antigen class I-restricted activation of CD8+ T cells provides the immunogenetic basis of a systemic drug hypersensitivity. *Immunity* 2008;**28**:822–32.
50. FDA Alert on 11/24/2008 Phenytoin (marketed as Dilantin, Phenytek and generics) and Fosphenytoin Sodium (marketed as Cerebyx and generics) – Healthcare Professional Sheet text version. Available at URL: http://www. fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm124788.htm, [search 26 Jan 2009].
51. Locharernkul C, Shotelersuk V, Hirankarn N. HLA-B∗1502 screening: time to clinical practice. *Epilepsia* 2010;**51**:936–8.
52. Cheng SH, Kwan P, Ng HK, et al. New testing approach in HLA genotyping helps overcome barriers in effective clinical practice. *Clin Chem* 2009;**55**:1568–72.
53. HLA Alleles associated with adverse drug reactions and methods for detecting such. Available at URL: http://www.surechem.org/index.php?Action=document&docld...db [search 16 Jun 2010].
54. Meador KJ, Baker GA, Browning N, et al. Cognitive function at 3 years of age after fetal exposure to antiepileptic drugs. *N Eng J Med* 2009;**360**:1597–605.