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Diagnostic Tests and Genetic Screening for Antiepileptic-Induced Severe Cutaneous Adverse Reactions (SCAR) in Resource Limited Setting

Chew Beng Hoong[1*], G Saravana Govindasamy[1*], Nur Fadhlina Musa[2], Dzul Azri Mohamed Noor[1], Nur Aizati Athirah Daud[1,2**]

[1]Discipline of Clinical Pharmacy, School of Pharmaceutical Sciences, Universiti Sains Malaysia, 11800 USM, Pulau Pinang, Malaysia

[2]Human Genome Center, School of Medical Sciences, Universiti Sains Malaysia, 16150 Kubang Kerian, Kota Bharu, Kelantan, Malaysia

Abstract

Objective: Several antiepileptic drugs (AEDs) may cause a wide array of severe cutaneous adverse drug reactions, regardless of the severity of epilepsy among the users. SCARs may cause implications in patient outcomes including hospitalization and economic implications. Preventive efforts using genetic screening for HLA alleles have been proposed to identify patients with a high risk of developing SCAR. However, genotyping costs posed a challenge in our country with resource limited settings (RLS). The objective of this review is to describe several aspects of AED-induced SCARs including the diagnostic tests, genetic and non-genetic risk factors, and the economic burden of HLA allele screening. This information was then used to propose a workflow for HLA testing in RLS. **Methods:** Article search was carried out using PubMed/MEDLINE, Science Direct, Google Scholar and Cochrane library from the year 1990 until 2020 using the key words 'cutaneous adverse drug reaction', 'genetic', 'epilepsy', 'antiepileptic' and 'HLA gene'. **Results:** Genetic predisposition is not the only factor associated with the incidence of SCARs. Stratifying the patients according to non-genetic risk factors, for example age, may provide a more selective screening for HLA alleles in RLS. HLA-B*15:02 screening before starting AEDs in Malaysia might be cost-effective when taking into account the shrinking cost-effectiveness threshold in our country, although, more pharmacoeconomic data are needed to draw a conclusion. **Conclusion:** Selected patient screening for HLA allele can be introduced in RLS in the prevention of AED-induced SCARs.

Keywords: Pharmacogenomics, antiepileptics, SCAR, genetic screening, resource limited setting

Introduction

The majority of adverse drug reaction events affects the skin, which is referred to as the 'cutaneous adverse drug reactions' (Mockenhaupt, 2017). The severity of cutaneous adverse drug reactions ranges from milder forms, such as urticaria, to severe forms, which are known as severe cutaneous adverse reactions (SCARs) (Su et al., 2016; Mockenhaupt, 2017). Drug-induced SCARs are immunologically mediated and classified as Type IV-delayed hypersensitivity reactions (Rive, Bourke and Phillips, 2013; Pavlos et al., 2014).

More than 85% of SCARs among the adult population are associated with drug use (Sassolas *et al.*, 2010; Mockenhaupt, 2017). Commonly implicated drugs in the incidence of SCARs include antimicrobials, antiepileptic drugs (AEDs) and antimetabolites (Sassolas *et al.*, 2010; Verma, Vasudevan and Pragasam, 2013; Pawar, 2015; Creamer *et al.*, 2016). Antimicrobials and AEDs jointly made up 75% of the total ADRs, which were reported over an approximate period of two years in Singapore. 95.7% of these ADRs were cutaneous ADRs of various severities and most of the SCARs event require prolonged hospitalizations and

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**Both authors contributed equally*

****Corresponding author:** Nur Aizati Athirah Daud
Discipline of Clinical Pharmacy, School of Pharmaceutical Sciences, Universiti Sains Malaysia, 11800 USM, Pulau Pinang, Malaysia
Tel: 604-6532412 **Email**: aizati@usm.my/aizati.daud@gmail.com

some were even life-threatening (Fiszenson-Albala *et al.*, 2003; Thong *et al.*, 2003). SCARs also cause economic burden in addition to being accountable for patient's suffering and hospital admission (Patel, Thakkar and Sharma, 2014).

The objective of this review is to describe several aspects of AED-induced SCARs, including diagnostic tests, genetic and non-genetic risk factors, the HLA genotype screening as prevention measures, and to propose a workflow of HLA testing in resource limited setting (RLS). Articles were searched in Pub Med, Science Direct, Google Scholar and Cochrane library from the year 1990 until 2020 using the key words 'cutaneous adverse drug reaction', 'genetic', 'epilepsy', 'antiepileptic' and 'HLA gene'.

Types of SCARs

SCARs are presented with a wide range of clinical manifestations and symptoms, which includes toxic epidermal necrolysis (TEN), drug reaction with eosinophilia and systemic symptoms (DRESS), Stevens-Johnson syndrome (SJS) as well as acute generalised exanthematous syndrome (AGEP) (Adler *et al.*, 2017). Even though the SCARs have a low incidence rate (2% to 3%) among hospitalised patients, they are accountable for a high mortality rate, which ranges from 10% to 40% (Chan, 1990; Dipascuale *et al.*, 2005; Wolf *et al.*, 2005). According to a study conducted in a tertiary hospital in Korea, a total of USD 752,067 was spent in the management of 73 patients with SCARs. In the same study, it was reported that prolonged hospitalisations significantly increased the healthcare cost of the patients with SJS, TEN and DRESS. This emphasizes that SCARs also pose a significant economic burden while causing health issues of serious concern (Yang *et al.*, 2019).

SJS and TEN usually arises from 4 days up to 4 weeks after exposure to the offending drug. Both SJS and TEN are clinically manifested by skin detachment. The portion of body surface area affected differentiates SJS from TEN. Skin detachment of less than 10% of the body surface area is defined as SJS while skin detachment of 30% or more of the body surface area is termed as TEN. SJS-TEN is the term given for skin detachment that involves 10% to 29% of the body surface area (Auquier-Dunant *et al.*, 2002; Verma, Vasudevan and Pragasam, 2013). Ocular symptoms, fever, skin pain, influenza-like illness and general physical deterioration are among the manifestations that occur prior to the dermatological manifestations (Duong *et al.*, 2017; Guvenir *et al.*, 2019). At the early phase of these cutaneous reactions, the erythematous, dusky-red, irregularly shaped eruptions are visible on the upper trunk, proximal extremities and face (Auquier-Dunant *et al.*, 2002). Impermanent renal or liver enzyme spike or epithelial necrosis of bronchial or digestive tract indicates the visceral involvement of SJS and TEN (Hung *et al.*, 2009; Devarbhavi *et al.*, 2016; Duong *et al.*, 2017).

For DRESS, onset ranges from 2 to 6 weeks after the exposure to an offending drug. The classical dermatological manifestations of DRESS includes pustules, distal edema, facial edema, purpura and erythroderma (Kardaun *et al.*, 2007; Verma, Vasudevan and Pragasam, 2013). Up to 2 weeks prior to the onset of dermatological symptoms, fever, influenza-like symptoms, pruritus, lymphadenopathy or burning pain may occur. Renal involvement in the form of interstitial nephritis is also noted in DRESS patients (Kardaun *et al.*, 2013; Verma, Vasudevan and Pragasam, 2013).

AGEP is a less serious form of cutaneous ADR compared to SJS, TEN and DRESS (Sidoroff *et al.*, 2007). The onset of AGEP varies from 2 to 11 days after offending drug exposure (Sidoroff *et al.*, 2007; Sidoroff, 2012). Dermatological manifestations of AGEP includes intertriginous erythema, non-follicular sterile pustules, edema and post-pustular pinpoint desquamation. Dermatological symptoms develop simultaneously with high fever (Verma, Vasudevan and Pragasam, 2013; Duong *et al.*, 2017). Although rare, the development of hepatitis, pneumonitis or nephritis may also be associated with AGEP (Choi *et al.*, 2010; Sidoroff, 2012; Hotz *et al.*, 2013).

Antiepileptic-induced SCAR

AEDs are widely used in patients suffering from epilepsy as the primary treatment option and are also commonly used for some non-epileptic neurological conditions such as trigeminal neuralgia. There are at least 15 AEDs in the global market, including carbamazepine, clobazam, valproate, topiramate, levetiracetam, lamotrigine, phenobarbital, gabapentin, oxcarbazepine, phenytoin, and vigabatrin (Alvestad, Lydersen and Brodtkorb, 2007a). AEDs exhibit great interindividual variability in terms of seizure control and the risk of developing adverse reactions (Balestrini and Sisodiya, 2018).

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AEDs may cause a wide array of cutaneous adverse drug reactions that may even lead to disability or death regardless of its indication or cause of treatment (Deng *et al.*, 2017; Özkaya and Kılıç, 2018). According to a study by H. Arif *et Al.*(2007), 15.9% of 1649 adults aged 16 years old or more and on any of the AED agents were reported to have a rash at any point during the data collection period (Arif *et al.*, 2007). Aromatic AEDs, such as primidone, carbamazepine, phenytoin, phenobarbital, lamotrigine, oxcarbazepine and eslicarbazepine are more prone to cause cutaneous ADRs compared to non-aromatic AEDs (Fowler, Bansal and Lozsádi, 2019). The clinical manifestations of SCARs usually arise within 1 to 8 weeks from the initiation of AED therapy (Chan, 1990).

Diagnostic Tests for SCARs

Drug causality assessment is crucial in the management of SCARs and also prevention of similar incidence in affected patients (Su *et al.*, 2016). The identification of a drug that causes hypersensitivity is essential as the re-exposure of the incriminated drug may lead to a high risk of mortality and morbidity. Several *in-vitro* and *in-vivo* tests are available and can be used to assess the patients' risk of drug hypersensitivity and also the severity (Bergmann and Caubet, 2019). *In-vivo* tests include drug provocation test, cutaneous test and patch test. Meanwhile, *in-vitro* tests include specific IgE tests, HLA screening, lymphocyte transformation testing, enzyme-linked immunospot assay and intracellular cytokine staining. In the context of patient exposure to direct risk, *in-vitro* tests for drug hypersensitivity reactions are advantageous over *in-vivo* tests. The most commonly used diagnostic test for Type IV (delayed hypersensitivity reactions) is the patch test. However, none of the tests for the diagnosis of Type IV hypersensitivity reactions has demonstrated a 100% sensitivity (Rive, Bourke and Phillips, 2013).

Cutaneous Tests

In cutaneous testing, a combination of skin prick testing (SPT) and intradermal testing (IDT) is used. Skin prick testing is usually carried out first due to a very minimal ADR risk. Intradermal testing presents a slightly higher risk of a severe form of ADR (Kränke and Aberer, 2009). In patients with bullous diseases, the use of delayed-reading intradermal tests is an absolute contraindication (Bergmann and Caubet, 2019). Patch testing is the diagnostic test of choice for delayed hypersensitivity reactions (Rive, Bourke and Phillips, 2013). It is also the primary diagnostic test for most SCAR patients (Bergmann and Caubet, 2019). The sensitivity of patch testing is reported to be 70% at most. Higher sensitivities were recorded for AGEP, SJS and DRESS associated with carbamazepine and fixed drug eruptions (Osawa *et al.*, 1990; Alanko, 1993).

Drug Provocation Test

The drug provocation test (DPT) is useful in identifying drug hypersensitivity reactions in the case of diminished sensitivity in skin testing (Rerkpattanapipat, Chiriac and Demoly, 2011). This test involves a controlled challenge with the suspected offending drug. Since SCARs are fatal, drug provocation test is to be avoided in patients with a previous history of SCARs or with other types of skin hypersensitivity (Bergmann and Caubet, 2019).

Lymphocyte Transformation Test

Lymphocyte Transformation Test (LTT) is useful in the identification of delayed hypersensitivity reactions. In this testing, peripheral blood mononuclear cells of a patient with a certain type of delayed hypersensitivity reaction are used for the isolation of lymphocytes, which are then cultured with the drug suspected to be causing such reaction. It may take up to a week to establish the results in the form of a stimulation index (Torres, Mayorga and Blanca, 2009). However, it is important to note that a negative outcome in LTT does not exclude any drugs tested (Rive, Bourke and Phillips, 2013).

Enzyme-linked Immunospot Assay and Intracellular Cytokine Staining

Enzyme-linked immunospot (ELISpot) assay and intracellular cytokine staining (ICS) are useful diagnostic tools for a variety of Type IV delayed hypersensitivity reaction phenotypes (Scheibenbogen *et al.*, 1997). Both are used to measure the production of target cytokines following exposure to suspected offending drugs. These tools are currently utilised for research purposes due to their expected durability of responses and sensitivities (Rive, Bourke and Phillips, 2013).

Specific IgE Test

Evidence of sensitisation to a specific antigen can be obtained through the detection of specific IgE

in serum. Such evidence can be correlated with a history of a hypersensitivity reaction in order to conclude the diagnosis of hypersensitivity reaction (Fontaine *et al.*, 2007). The specific IgE detection in serum provides high specificity results but lacks in sensitivity (Rive, Bourke and Phillips, 2013). Based on the diagnostic tests discussed briefly above, their applicability can be classified according to a few common types of SCARs as shown in Table 1 (Rive, Bourke and Phillips, 2013).

Genetic markers of AED-induced SCARs

The incidence of SCARs is greatly associated with genetic predisposition (Mockenhaupt, 2017). The core principle in finding the pharmacogenetic markers related to ADRs is to recognise the right phenotypic entity with specificity, which is responsible for the incidence of ADRs. The presence of specific alleles in human leukocyte antigen (HLA) alleles is the primary reason for the incidence of SCARs. Viral infection and disruption in drug clearance are among other factors that may lead to the incidence of SCARs (Su *et al.*, 2016).

HLA alleles are correlated with certain SCAR types in relation to specific drugs. It is important to take note that the association between HLA alleles and SCARs is unique according to ethnicities. Thus, an association between HLA alleles and SCARs in one specific ethnicity may not apply to other ethnicities (Jung *et al.*, 2018). HLA-B alleles also possess functional roles in the pathogenesis of certain diseases (Chung *et al.*, 2008). Pharmacogenetic markers described in the literature are mostly associated with delayed ADRs such as SJS and TEN. The information and knowledge on pharmacogenetics of IgE-medicated ADRs are sparse (Guéant-Rodriguez *et al.*, 2008). The association of certain HLA alleles with IgE-mediated ADRs has not been reported (Phillips *et al.*, 2011). Comprehensible diagnostic criteria together with a meticulous systematic approach to phenotyping can minimise the undetermined or overlapping cases of SCARs (Phillips *et al.*, 2011).

Table 1. The applicability of diagnostic tests for several types of AED-induced SCARs (Rive, Bourke and Phillips, 2013)

Diagnostic Tests	SJS/TEN	AGEP	DRESS
Patch Test	Low sensitivity	Applicable	Applicable
Cutaneous Tests	Low sensitivity	Applicable but IDT reading is delayed	Applicable but IDT reading is delayed
Drug Provocation Test	Not applicable	Not applicable	Not applicable
Lymphocyte Transformation Testing	Applicable	Applicable	Applicable
Enzyme-linked Immunospot Assay & Intracellular Cytokine Staining	Applicable	Applicable	Applicable
Specific IgE Screening	Not applicable	Not applicable	Not applicable
HLA Screening	Applicable	Not applicable	Applicable

Abbreviation: SJS: Stevens-Johnson Syndrome; TEN: toxic epidermal necrolysis; AGEP: acute generalised exanthematous syndrome; DRESS: drug reaction with eosinophilia and systemic symptoms

The discovery of genetic markers has improved the incidence of SCARs in several countries. The role of genetic markers was deemed as preventive measures against the development of SCARs in susceptible individuals. It is known that the prompt withdrawal of the offending drug remains the primary treatment option rather than treating the cutaneous manifestations without discontinuing the offending agent (Su *et al.*, 2016). Randomised controlled trials (RCTs) on the effectiveness of HLA screening before the initiation of AEDs is very challenging, due to the rare incidence of SCARs (Alfirevic *et al.*, 2019).

The most common allele markers associated with SCARs are HLA-B*15:02, HLA-B*15:13, HLA-B*15:21 and HLA-A*31:01; each is prevalent in different populations (Amstutz *et al.*, 2013; Chang *et al.*, 2017; Jaruthamsophon *et al.*, 2017). For example, the alleles in B*15 lineages are more prevalent in northeast Asia (Dean, 2012). Among the Southeast Asians, the prevalence of HLA-B*15:02 allele was reported to be at 8.0% (Chung et al., 2004; Gonzalez-Galarza et al., 2011). The association between the HLA-B*15:02 and carbamazepine-induced SJS/TEN was first reported by Chung *et al*. (2004) in a study involving Han Chinese populations living in Taiwan (Chung *et al.*, 2004). A systematic review and meta-analysis of 16 articles showed that there is a strong association between carbamazepine-induced SJS/TEN and HLA-B*15:02 allele, especially in the Asian population (Tangamornsuksan *et al.*, 2013). The risk of carbamazepine-induced SJS/TEN is relatively higher in Han Chinese, Thai, Korean and Malaysian Malay populations as these populations possess high HLA-B*15:02 allele frequencies (Tangamornsuksan *et al.*, 2013).

The HLA-B*15:02 allele has also been associated with SJS/TEN induced by other aromatic amines AEDs with structural similarity to carbamazepine (Man et al., 2007; Lin et al., 2009). In the Han Chinese population, the combination of HLA-A*0201/C*1502 alleles are associated with an increased risk of DRESS induced by phenytoin (Hung *et al.*, 2010). However, lamotrigine has not been associated with HLA-B*15:02 in the same population (Hung *et al.*, 2010). HLA-A*3101 is associated with SCARs induced by lamotrigine in the Korean population (Kim *et al.*, 2017), meanwhile HLA-B*3801 and HLA-A*2402 are associated with lamotrigine-induced SJS/TEN and DRESS, respectively, in the Spanish population (Ramírez *et al.*, 2017). In the European population, lamotrigine-induced SCARs were reported among patients with HLA-A*6801, B*5801, DQB1*0609, DRB1*1301 and C*0718 alleles. These associations warrant further confirmation via larger, independent sample studies (Kazeem *et al.*, 2009). Studies done among Caucasian populations suggest that the HLA-B*07:02 allele possesses protective property against the incidence of carbamazepine-induced DRESS (Romano *et al.*, 1998; Pirmohamed *et al.*, 2001).

Pre-emptive HLA genotype screening for SCARs

HLA screening is beneficial to prevent the incidence of drug hypersensitivity syndromes (Rive, Bourke and Phillips, 2013). Studies also reported a 100% negative predictive value for HLA-B*15:02 allele for SJS/TEN associated with carbamazepine (Kim *et al.*, 2011; Ozeki *et al.*, 2011, Pavlos, Mallal and Phillips, 2012). The Food and Drug Administration (FDA) of the United States has recommended routine screening for the HLA-B*15:02 allele in high-risk individuals of Southeast Asian native ('FDA, 2008; Ferrell and McLeod, 2008). Meanwhile, in Taiwan, pre-emptive screening for the HLA-B*15:02 allele upon the initiation of certain AEDs has been implemented. This screening had been shown to significantly reduce the incidence of SCARs associated with carbamazepine, therefore reducing the medical costs associated with this reaction (Chen *et al.*, 2011). In Singapore, the pre-emptive HLA-B*15:02 genotyping among newly diagnosed epilepsy patients was shown to be cost-effective in two out of three ethnic groups studied. This suggests that genotyping the risky allele may be cheaper than the cost of treating SCARs if it occurs (Dong, Sung and Finkelstein, 2012). More details on the pharmacoeconomic evaluation were discussed in the later section of this review.

Recent emerging techniques such as next-generation sequencing and genome-wide association studies (GWAS) are anticipated to boost genomic studies involving ADRs (McCormack *et al.*, 2011; Ozeki *et al.*, 2011). With more pharmacogenetic studies, more genetic markers in AEDs-induced SCARs can be identified and utilised to ease the identification process of high-risk patients. This will also deepen the understanding of ADRs pathogenesis and also will lead to reduced healthcare costs (Jung *et al.*, 2018).

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Table 2. Summary of few regional studies on the association between HLA-B*15:02 and AED-induced SCARs

Study	Population (Country)	Odds ratio, OR (95% CI)
(Chung *et al.*, 2004)	Han Chinese (Taiwan)	OR: 2504 (95% CI: 126 – 49,522)
(Chang *et al.*, 2011)	Malays (Malaysia)	OR: 16.15 (95% CI: 4.57 – 62.4)
(Man *et al.*, 2007)	Han Chinese (Hong Kong)	OR: 17.60 (95% CI: 2.90 – 105.2)
(Kim *et al.*, 2011)	Koreans (South Korea)	OR: 6.4 (95% CI: 0.30 – 164.3)
(Tassaneeyakul *et al.*, 2010)	Thai (Thailand)	OR: 54.76 (95% CI: 14.62 – 205.13)
(Locharernkul *et al.*, 2008)	Thai (Thailand)	OR: 52.76 (95% CI: 2.70 – 1031.31)
(Chong *et al.*, 2014)	Malay, Chinese and Indians (Singapore)	OR: 27.20 (95% CI: 2.67 – ∞)

Non-genetic risk factors in AED-induced SCARs

Although HLA screening is a useful preventive step for AED-induced SCAR, it is not a routine practice in most countries due to the complexity of healthcare resource allocation (Ransom and Olsson, 2017). Looking at various genetic determinant in AED-induced SCAR reaction (Rufini *et al.*, 2015), only patients receiving carbamazepine is currently recommended to undergo HLA-B*15:02 testing, especially for Chinese and Malay ethnicities (Raymond, Azman Ali, 2017). However, this may not be ideal for countries with a smaller portion of at-risk ethnicities. For example, one cohort study done in the United State has shown that a significant number of HLA-B*15:02 carriers was reported to have non-Asian ethnicity, which mean screening HLA*B15:02 to prevent carbamazepine induced adverse reaction should not be restricted to patients with Asian ancestry because it may not identify a large portion of at-risk patients (Fang *et al.*, 2019).

Since much evidence have also shown the involvement of alleles other than HLA-B*15:02 in the risk of SCARs, questions may arise on the necessity to screen for other alleles too before the patients can safely be started with AEDs. Economic modelling on universal screening on HLA-B*15:02 has shown inferior result in our country as well (Chong *et al.*, 2017). Another unanswered question is, who is the better candidate to go on genetic testing before starting AED? This led to the interest in looking at other determinants or risk factors, which will help to prioritize the testing in RLS.

Age and gender

Age is one of the factors that may determine the occurrence of many drug reactions (Błaszczyk, Lasoń and Czuczwar, 2015). In general, children have a higher tendency to have a reaction towards a medication compared to adults. This is due to their higher rates in metabolism that leads to increased reactive metabolites production (Zaccara, Franciotta and Perucca, 2007). A study by Hikino *et. al*. (2021) has reported on the characteristics of paediatric patients who developed AED-induced adverse reactions. It was shown that 75% of the cutaneous reactions occurred among paediatric patients with a mean age of 5.7 ± 4.7 years old (ranged 0 to 16 years old) (Hikino *et al.*, 2021).The youngest patient who had been reported to develop such reaction was 3 months old, as reported by Egunsola *et. al* (Egunsola *et al.*, 2018). Moreover, one study showed that the incidence of SCAR is 10 times higher to occur among children taking lamotrigine compared to adults (Mockenhaupt *et al.*, 2005).

In addition to differences in metabolic capacity, the risk of AED-related cutaneous adverse reactions increased with age within the adult population (starting from 16 years old onwards) (Alvestad, Lydersen and Brodtkorb, 2007b). In the adult population, the hormonal factor plays an important role in this reaction, in contrast to the role of metabolic capacity in the paediatric population. This can be explained by patients' characteristics in the majority of genetic association studies as shown in Table 3. Most studies excluded the paediatric population due to ethical issues involving vulnerable groups with the inability to consent. Judging from reported cases of AED-related cutaneous adverse reactions over the past 2 decades, the age can range from as low

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as 3 months old up to the geriatric population of 88 years old (Hsiao *et al.*, 2014; Egunsola *et al.*, 2018).

From a pharmacokinetic point of view (Mani *et al.*, 2019), hypersensitivity reaction occurred more frequently in a particular age of life, however, AED-induced SCAR may occur in any stage of life regardless of age . Having said that, managing AED-induced SCAR in paediatric and geriatric populations poses some challenges. Approximately 1 out of 150 children is diagnosed with epilepsy during the first 10 years of life, with the highest incidence rate observed during infancy (Aaberg *et al.*, 2017). Given the nature of epilepsy and the onset of seizures, which may occur and be diagnosed at an early age, many paediatric patients were started on any of the AEDs. Recognition and treatment of dermatological emergencies such as SJS/TEN from other paediatric rash is often ambiguous for paediatricians (Reynolds *et al.*, 2021). It also showed that managing SJS/TEN in the paediatric population has contributed to a substantial healthcare burden (Hsu *et al.*, 2017) .

On the other hand, for the elderly population, complications from AED therapy may likely be related to multi-organ involvement, taking into consideration other issues related to polydrug interaction and side effects (Shanbhag *et al.*, 2020). It has been reported that elderlies with the age of 50 years or older have experienced a higher rate of medication-induced skin reaction (Alvestad, Lydersen and Brodtkorb, 2007a). Comorbidities and hospital-related complications of SJS/TEN in the elderlies (≥ 65 years old) are significantly higher compared to non-elderly patients (Patel *et al.*, 2019). To prevent the occurrence of carbamazepine-induce SCAR in countries with limited pharmacogenomics centres offering HLA-B*15:02 testing such as Malaysia (Raymond, Azman Ali, 2017), we suggest patients below 18 years old (as defined by paediatric service in Ministry of Health, Malaysia) and patients more than 65 years old (as defined by geriatric service in Ministry of Health, Malaysia) can be prioritized for HLA-B*15:02 pre-emptive screening to prevent carbamazepine-induced SCAR.

The role of gender in the incidence of SCARs have been studied before. Female and male hormones influence one of the most important cell line production in SCAR, which is the T-cell (Alvestad, Lydersen and Brodtkorb, 2007a). Females seem to be at a higher risk than males, particularly in fertile age (Alvestad, Lydersen and Brodtkorb, 2007a). Results from a nationwide study in Korea did not show any gender difference between the phenotypes of SCARs evaluated (Kang *et al.*, 2021). In addition, one study showed that gender is not a predictor of mortality in the incidence of SCARs (Hsu *et al.*, 2016). Therefore, at this stage, gender should not be one of the factors to consider screening prioritization.

Genetic testing in resource limited setting (RLS): What data do we have?

Personalized medicine (PM) has been slowly evolving from the past decades, and finding new biomarkers are one of the main focus in the genetic field (Agyeman and Ofori-Asenso, 2015). From the first discovery of HLA (Thorsby, 2009) to the theoretical aspect paper published in the 1980s on the discovery of HLA-B*15:02 (Thomson, 1981) until now, at least 5 additional alleles have been identified as potential genetic risk factors of developing SCARs (i.e. HLA-B*15:01, HLA-B*15:11, HLA-A*02:01, and HLA-DRB1*01:01, HLA-A*24:02) over the past 30 years (Mani *et al.*, 2019).

Practicing personalized medicine in a resource-limited setting is a challenge. Knowing other non-genetic risk factors associated with the risk may facilitate the selection of patients who need further genotyping. Moreover, genetic testing of RLS, for example, HLA-B*15:02, is only available in limited facilities, it is costly and the process from receiving blood sample until the result reported may take up to 3 weeks, as mentioned in the Consensus Guideline of Management of Epilepsy 2017 (Raymond, Azman Ali, 2017). In business market analysis, the more specific a product can achieve an outcome, the higher the price (Anderson and Wynstra, 2010). This also applies to PM; the more precise a diagnostic test or a treatment is, the higher the cost to our healthcare system. From the pharmacoeconomic perspective, one major concern arises with PM is whether, it is worthy to allocate such financial allocation for PM, especially in low willingness-to-pay threshold country (Chong *et al.*, 2017). Furthermore, in RLS, the major challenge is a social-political issue when it comes to research and healthcare allocation followed by human resources (Peñas-LLedó *et al.*, 2020).

Table 3. Summary of Reported Age during Cutaneous Reaction Presentation in Genetic Association Studies

Study	Ethnicity	Allele	Number of study population/ patient	Gender (Male/Female)	Age (mean years ± SD, range)
(Xu *et al.*, 2019)	Eastern Han Chinese	HLA-A*32:01	30	16/14	18.57 ± 12.80 years, 2 – 44
(Jaruthamsophon *et al.*, 2017)	Thai	HLA-B*15:21	1	1/0	Case report:14
(Chang *et al.*, 2017)	Malaysian	HLA-B*15:02 HLA-B*15:13	16	7/9	Not reported
(Zeng *et al.*, 2015)	Han Chinese	HLA-B*15:02	12	6/6	25.3 ± 9.2, 12 – 41
(Hsiao *et al.*, 2014)	Han Chinese	HLA-B*15:02	194	102/92	49.2 ± 18,7 – 88
(Cheung *et al.*, 2013)	Han Chinese	HLA-B*15:02 HLA-B*13:01 HLA-A*40:01	55	25/30	38 ± 17, 6 – 77
(Kulkantrakorn *et al.*, 2012)	Thai	HLA-B*15:02	34	10/24	47.0 ± 14.7,20 – 78
(Kim *et al.*, 2011)	Koreans	HLA-B*15:02 HLA-B*15:11	24	13/11	52.1 ± 15.1, 23 – 80
(Then *et al.*, 2011)	Malaysian	HLA-B*15:02	19	9/10	18.32 ± 13.28,1 – 49
(Chang *et al.*, 2011)	Malaysian	HLA-B*15:02	16	Not reported	Not reported
(Ozeki *et al.*, 2011)	Japanese	HLA-A*31:01	First study:61 Replication study: 16	Not reported	First study: 54 (median), 12 – 82 (range) Replication study: 61 (median), 24 – 74 (range)
(McCormack *et al.*, 2011)	Europeans	HLA-A*31:01	145	Not reported	Not reported
(Min *et al.*, 2011)	Han Chinese	HLA-B*15:02	2	1/1	2 Case Reports: 29 & 77
(Mehta *et al.*, 2009)	Hindu Indian	HLA-B*15:02	8	4/4	22.88 ± 10.46, 10 – 45
(Kazeem *et al.*, 2009)	Europeans	HLA-A*68:01	22	9/13	32 ± 18, 6 – 70
(Kashiwagi *et al.*, 2008)	Japanese	HLA-A*31:01	22	Not reported	Not reported
(Locharernkul *et al.*, 2008)	Thai	HLA-B*15:02	10	7/3	**12.9 ± 4.74, 6 – 20
(Lonjou *et al.*, 2006)	Europeans	HLA-B*38	12	8/4	45.33 ± 12.27, 31 – 74
(Alfirevic *et al.*, 2006)	Caucasians	HLA-B*07:02	56	Not reported	Not reported

*n = Number of cases reported

**the onset of SCAR/cutaneous reaction was not defined

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For a better understanding of the parameter in economic evaluation modelling, the results of economic evaluations, especially cost-effectiveness analysis and cost-utility analysis, are usually summarized as an incremental cost-effectiveness ratio (ICER). The ICER represents the incremental cost per incremental gain in the outcomes of one intervention compared to another. To conclude the cost- effectiveness (CE) of health care interventions, the ICER is usually compared to a reference value, the CE threshold, which is sometimes referred to as the ICER threshold or the ceiling threshold (Lim *et al.*, 2017). The CE threshold represents the willingness to pay per quality-adjusted life-year (WTP/QALY) gained and is a vital component of decision making involving economic evaluation (Lim *et al.*, 2017).

To our best search, all cost-effectiveness studies are using carbamazepine as a causative agent to design an economic model. Although most of the studies shown in Table 4 conclude the screening of HLA-B*15:02 is cost-effective, the ICER obtained is still close to the CE threshold. Some factors affects the CE thresholds which leads to CE threshold changes along with situations in a particular country, for example, education level, estimated monthly household income, and the description of health state scenarios (Lim *et al.*, 2017). The CE threshold recommended by World Health Organization (WHO) in 2005 [1 to 3 times gross domestic product(GDP) per capita per disability-adjusted life years], does not accurately reflect the specific needs as well as the economic and disease burden of the general population in each country (Lim *et al.*, 2017).

Table 4. Summary of outcome from cost-effectiveness study on AED in various country

Study	Year	Country	Screening method	Treatment Strategies in Modelling	Primary Outcome
(Dong, Sung and Finkelstein, 2012)	2012	Singapore	Universal	First Line: Carbamazepine/ phenytoin Alternative (if cannot tolerate first line): Sodium valproate	CE Threshold: USD 50,000/QALY ICER(USD/QALY): Chinese (37,030), Malay (7,930), Indian (136,630)
(Rattanavipapong *et al.*, 2013)	2013	Thailand	Universal	First line: Carbamazepine Alternative: Sodium valproate	CE Threshold: THB120,000/QALY ICER(THB/QALY): Epilepsy model-222,000
(Plumpton *et al.*, 2015)	2015	United Kingdom	Routine	First Line: Lamotrigine prescribed for patients who test positive versus carbamazepine prescribed without testing.	CE Threshold: £20,000QALY/ ICER(£/QALY): 12,808

				Alternative: Sodium valproate	
(Chong *et al.*, 2017)	2017	Malaysia	Universal	First line: Carbamazepine Alternative: Sodium valproate/ topiramate	CE Threshold: MYR 37 000 (USD 8982)/ QALY ICER(MYR/QALY): The treatment strategy incurred more costs but resulted in lower QALYs than that of current practice.

HLA-B*15:02 screening prior to initiation of carbamazepine: Beyond Neurology Medication Therapy Adherence Clinic (MTAC)

It is reported that the CE threshold in Malaysia is lower (parametric interval regression model was MYR19,929 to MYR28,470) in 2017 than the CE threshold used by Chong et al in 2015 (MYR37,000) (Lim *et al.*, 2017). This means that HLA-B*15:02 screening before starting CBZ in Malaysia might be cost-effective if we take into account of the shrinking of the CE threshold in our country. From a practical point of view, the current CE study is not enough to justify the healthcare allocation for routine genetic screening before starting AED (Ransom and Olsson, 2017). Other than that, the use of AED is changing following the new guideline recommendations. Hence, a more comprehensive and updated pharmacoeconomic study with revised CE threshold is needed to help in the decision making.

HLA-B*15:02 screening prior to initiation of carbamazepine: Beyond Neurology Medication Therapy Adherence Clinic (MTAC)

Pharmacist-led Medication Therapy Adherence clinics (MTAC) are well established in some areas of ambulatory care and have been beneficial in the treatment aspect of patients by improving drug compliance, decreasing inappropriate prescribing and providing positive therapeutic outcomes by monitoring patients' treatment plans. In Malaysia, several MTAC clinics have been established, especially for chronic diseases like diabetes, retroviral disease, respiratory diseases and neurologic disorders. In Neurology MTAC, clinical pharmacists have played an important role in the medication assessment, dose adjustments, monitoring and counseling for patients with epilepsy, stroke and Parkinson's disease (Roshayati binti Mohamad Sani,Rozita binti Mohamad,Nor Hasni binti Haron, 2019).

Neurology MTAC is a good platform to initiate a point-of-care HLA testing for newly treated patients. This will be an initiative to implement current knowledge in precision medicine in the prevention of AED-induced SCARs. Patients may be prescribed with drugs according to their HLA-B*15:02 results and other non-genetic risk factors. The genetic information gives an added value to the patient input, as well as facilitating the healthcare team in medication therapy management (Mills and Haga, 2013). Taking into account of age in prioritization of screening and shrinking CE threshold in RLS, we proposed an algorithm of patient eligibility for point-of-care genetic testing before the initiation of carbamazepine or other risky AEDs (Figure 1). An informed decision-making about genetic testing is one of the keys of an effective genetic testing service, therefore a collaborative effort with other health care professionals like physicians and genetic counsellors (if available) is crucial (Newman *et al.*, 2012). Genetic counselors play a role in informing and assisting physicians in the interpretation and communication of genetic test results, meanwhile pharmacists will provide therapeutic advice on drug selection, dosage adjustment and drug monitoring based in patients' genetic and non-genetic factors (Mills and Haga, 2013, Burns, 2008).

In this proposed algorithm, patients planned to be initiated with carbamazepine will be screened for

eligibility for genetic testing (Figure 1). Those aged less than 18 years old and more than 65 years old, and patients with a history of drug allergies (at any age) are prioritized for HLA-B*15:02 allele testing. For patients with HLA-B*15:02 positive, carbamazepine should be avoided and started with alternative AED based on safety and type of seizures. As recommended by the Consensus Guideline in the Management of Epilepsy, alternative AEDs include sodium valproate for generalized onset epilepsy and levetiracetam for focal onset epilepsy. For the management of trigeminal neuralgia, carbamazepine can be replaced by gabapentin (Yuan *et al.*, 2016). Counselling on the risk of SCARs after carbamazepine initiation is still needed if the patient is tested negative because the latency period for carbamazepine-induced SCAR is between 25 – 90 days. Patients who are already on carbamazepine after 3 months without SCAR should be safe to continue with the treatment (Raymond, Azman Ali, 2017). This proposed workflow process can serve as a novel idea in setting up future PM services in RLS.

Future perspective

Despite a strong association between HLA alleles and the risk of developing carbamazepine-induced SCARs in Asian ethnicity, HLA allele testing is not mandatory or recommended by local agencies in majority of the countries in Southeast Asia. Among the major challenges in the implementation of genetic testing is the lack of guidelines and/or consensus documents in clinical management of SCARs (Jantararoungtong *et. al.,* 2021). There is also a gap in collaborative network among researchers in this region to facilitate the harmonisation of workplan for such guideline. For the implementation of genetic testing in clinical settings, the keys for success include state-of-the-art facilities and a great effort from a multidisciplinary team. An economic evaluation on the costs and outcomes of point-of-care genetic testing should be done on a national level to provide a supporting input on the future direction of this health care intervention especially in RLS.

Conclusion

Management of SCAR and genetic testing both contribute to a significant amount of healthcare burden. To date, genetic screening to prevent AED induced SCAR is only recommended but not a routine practice in most of healthcare facilities around the world, due to lack of evidence that it is cost-effective. There is still lack of prospective study to correlate the results from genetic association studies to economic evaluation in genetic screening. Judging from the potential risk factor of SCAR on certain age range of patient, selected screening for HLA-B*15:02 can be started with pediatric (≤ 18 years old) and geriatric (≥ 60 years old) patients in an effort to reduce the incidence of SCAR in RLS.

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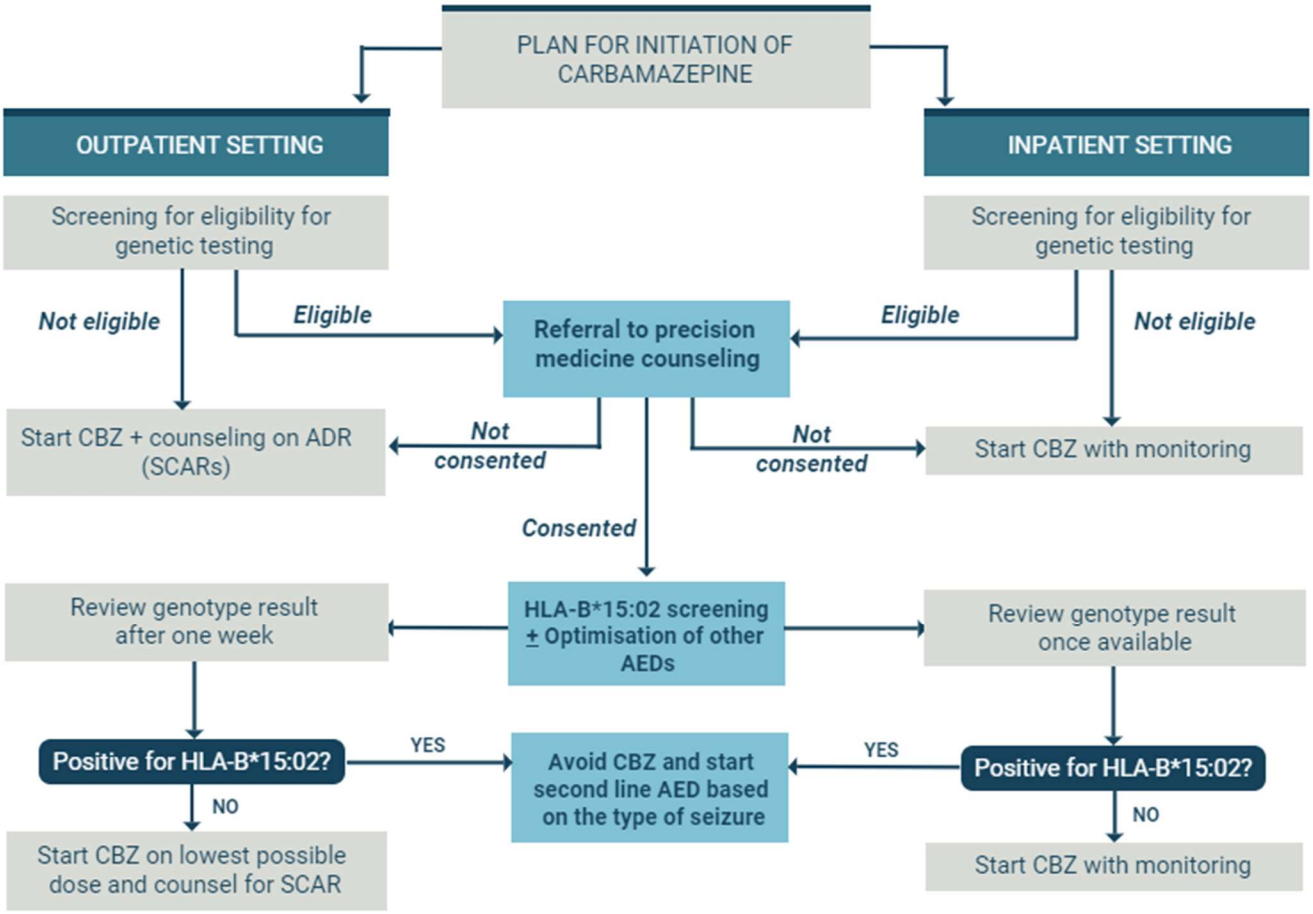

Figure 1. Proposed workflow for HLA-B*15:02 screening service.
Abbreviation: ADR: adverse drug reaction; AED: antiepileptics; CBZ: carbamazepine; SCAR: severe cutaneous adverse reaction

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Conflict of interest

The authors declare that there is no conflict of interest.

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