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Association of HLA Alleles with Anti-Epileptic (Carbamazepine and Phenytoin) in Inducing Steven Johnson Syndrome or Toxic Epidermal Necrolysis: A Narrative Review

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Adverse drug reaction (ADRs) remains a concern among the healthcare providers because of its unpredictable nature and the possibility to be life-threatening if left untreated. Carbamazepine and Phenytoin are commonly known to cause Steven-Johnson Syndrome (SJS) and Toxic Epidermal Necrolysis (TEN). This report aims to summarise on Carbamazepine and Phenytoin -induced SJS/TEN and its association with HLA genes. It is apparent that HLA-B*15:02 and HLA-B*31:01 were the most important alleles responsible for SJS/TEN in reaction to Carbamazepine and Phenytoin. Together with suspected alleles and antiepileptics, a person may have a greater risk of experiencing ADRs rather than those people who do not carry any of the alleles. Pharmacogenetic testing can be implemented in clinical practices before prescription of these two antiepileptics to avoid such reactions.

Keywords: carbamazepine; HLA alleles; phenytoin; Steven Johnson Syndrome; Toxic Epidermal Necrolysis

I. INTRODUCTION

Adverse drug reaction (ADR) is an unintended effect from a therapy. It became one of the pressing reasons for morbidity and mortality. In Europe, about 197,000 people died every year due to ADRs (Abdul Hadi *et al.*, 2017). According to the WHO, ADRs are an unwanted and undesirable effect that can be observed because of exposure to medical products regardless of a single or a combination use of drugs. Medication errors, prescriber error and negligence may precipitate the ADR (Khalil & Huang, 2020). About 5% of ADRs reported are due to hospitalisation and about 10% to 20% of patients get ADRs during hospitalisation (Giardina *et al.*, 2018). Rapid trend of polypharmacy, an increase in the number of drugs in the market and an aging population can contribute to the prevalence of ADRs in the world. ADRs can be prevented but depends on the type of exposure and the acuteness of the case. However, it is difficult to determine the exact trigger of an ADR (Pande, 2018).

Steven Johnson Syndrome (SJS) and Toxic Epidermal Necrosis (TEN) are considered as life-threatening diseases. Both are considered similar but different in the total area of skin detachment. At least 1 to 10% of skin detachment manifested in SJS meanwhile TEN is the diagnosis for more than 30% of total skin detachment. Overlapping frequency in both diseases is about 10 to 30 % of total area skin detachment (Klimas *et al.*, 2015). These conditions are dangerous as protective barriers of the skin are damaged, leading to extreme loss of fluid from the body. An infection may develop and in the worst case it can lead to death. In the earlier phase, common symptoms like fever, stinging in the eyes and feeling discomfort in swallowing can be observed followed by cutaneous manifestations after a several days (Klimas *et al.*, 2015). Initial sites involving the face and the trunk to some extend can affect the respiratory and the digestive tracks. Signs like oedema, erythema that involve the ocular and buccal can be seen in more than 90% of patients and the onset duration is frequent (Klimas *et al.*, 2015). In a later phase, clinical

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manifestation like necrotic and detachable skin can be observed (Fakoya *et al.*, 2018). It was observed that it takes about 2 to 8 weeks for the onset of these disease to happen after drug intake (Flowler *et al.*, 2019)

Global incidence for SJS is estimated to range from 1.0 to 6.0 million while 0.4 to 1.2 million demonstrated TEN (Yang *et al.*, 2018). Nevertheless, a study revealed the risks for both diseases increase among the Asian population compared to Caucasian (Yang *et al.*, 2018). People of African ancestry also face greater risk, similar to people of Asian population (Frey *et al.*, 2017). In Malaysia, a 10-year study showed that the mortality rate from TEN and SJS are 13.3% and 1.9% respectively (Loo *et al.*, 2018).

A. Risk Factors and Causes

Besides ethnicity, it is reported that people between the ages of 21 to 40 years old can easily be exposed to SJS/TEN compared to people aged more than 60 years old with 46.1% and 6.1% respectively (Irungu *et al.*, 2017). Different study in United Kingdom showed contradicting results where children from the age of 1 to 10 years old and adults above 80 years old are highly exposed to both diseases with the incidence rate (IR) being reported to be 7.63 to 8.97 and 8.75 per million people respectively (Frey *et al.*, 2017). Similar results are seen in the Korean Population while United State reported higher IR with 12.7 cases per million people (Frey *et al.*, 2017; Yang *et al.*, 2016). In term of gender, female is highly susceptible to these hypersensitivity reactions compared to male with a ratio of 2.1 respectively (Irungu *et al.*, 2017). Similar ratio is seen for TEN cases with where female still predominate male cases observed in Japan (1:07 ratio) (Yamane *et al.*, 2016). In United Kingdom, the number of cases by sex is almost even where 50.1% cases involve male patients (Frey *et al.*, 2017). This showed different countries reported different epidemiology and incidence rate. Interestingly, winter seasons from December to February recorded higher IR (7.21) according to Clinical Practices Research Datalink (CPRD) (Frey *et al.*, 2017).

Most of the SJS/TEN incidence reported primarily related to medication (80% of cases) [16]. Antiepileptic is the second cause after antibiotic (24.1% and 29.5% respectively) [10]. It is important to note that a Kenyatta National Hospital observation found that trimethoprim is the common antibiotic that cause both SJS and TEN (22.9%) while antiepileptic like Carbamazepine is the cause of about 4.6% of cases respectively (Irungu *et al.*, 2017). A Chinese population study reported that more than 75% of 49 patients experience TEN after being prescribed with antibiotics meanwhile antiepileptic only cause about 24.1% of cases (Yang *et al.*, 2018). A small number of SJS/TEN incidences are due to infections like mycoplasma pneumonia and herpes simplex virus only contribute 5.2% while at least 3.5% of the cases are cause by HIV respectively (Irungu *et al.*, 2017; Ricardo *et al.*, 2018). Vaccination, on the other hand rarely cause SJS/TEN but could be due to limited reports (Chahal *et al.*, 2018).

In most cases, genetics has been suspected to play an important role in ADRs (Micaglio *et al.*, 2021). A gene in chromosome 6 encodes for a protein known as Human Leukocyte Antigen (HLA). It is expected to be responsible for triggering the immune response. HLA compatibility is also an important factor to consider in transplantation antigen. There are two classes of HLA identified; Class I and Class II which are composed of three regions like HLA-A, HLA-B and HLA-DR (Wieczorek *et al.,* 2017).

B. Diagnostics and Treatments

Diagnosing SJS and TEN is quite challenging since the clinical manifestations is quite similar with maculopapular exanthema and erythema multiforme (Hasegawa & Abe, 2020). Previously, granulysin has been used as early diagnosing tool to diagnose SJS/TEN (Hema *et al.*, 2019). More recent studies have proposed the potential biomarkers for SJS/TEN are Galectin-7 and Receptor Interacting kinase 3 (RIP3) (Hasegawa & Abe, 2020). Since SJS/TEN is characterised by the death of keratinocytes, mechanism of cell death can be necroptosis or apoptosis. In general, galectin-7 is a protein serum that takes part in apoptosis pathway where the overexpression of it results in keratinocyte apoptosis in SJS/TEN (Hasegawa *et al.*, 2020).

Overexpression of RIP3 can also produce similar result. Nevertheless, both biomarkers still need further refinement since it is yet to be established in clinical practices (Hema *et al.*, 2019). SCORTEN score for instance, is an establish method in which based on the score that will determine the mortality rate. This method will assess according to seven risk factors which include age over 40, heartbeat more than 120 beats per minutes, blood glucose level higher than 14 mmol/L, blood urea level more than 10 mmol/L, bicarbonate level less than 20 mEq/L, presence of cancer and total area detachment. Greater mortality rate (90%) will be predicted if a candidate scores more than 5 risk factors (Hasegawa *et al.*, 2020).

Early identification and withdrawal of the causal drugs are considered as the initial steps in taking care of the SJS and TEN patients. Some of the recommended approaches include supportive care, wound care, nutrient and fluid/ electrolyte balance (Schneider & Cohen 2017). Apart from the general measures, medical management like cyclosporin, corticosteroid, intravenous immunoglobulin (IVIG), Tacrolimus and Plasmapheresis also can be initiated to treat SJS/TEN (Papp *et al.*, 2018). Administration of corticosteroid can improve overall outcome if early treatment is initiated (Kumar *et al.*, 2018). Reducing inflammatory cytokine, survival rate among TEN patients also have been improved in treatment involving Methylprednisolone. Different study reported corticosteroid able to treat at least 71.4% of the SJS/TEN patient (Papp *et al.*, 2018). If someone is treated with dexamethasone, increasing the dose gradually by 4 mg is needed if the condition does not improve. Contradicting result is observed in another study where initiating corticosteroid can prolong hospitalisation stay and worsen infection condition (Kumar *et al.*, 2018). The use of corticosteroid can be considered effective only in large group of SJS/TEN survival patients (Ricardo *et al.*, 2018).

Cyclosporin A at dose of 3 to 5 mg/kg demonstrated a reduction in the progress of both diseases (Schneider & Cohen, 2017). It is a potent inhibitor of Interleukin-2 (IL2) that can indirectly target the T cell function and stop apoptosis process (Chen *et al.,* 2017). It worked by preventing Cytotoxic T cell and Fas-Fas ligand from causing the apoptosis (Chen *et al.*, 2017). Mortality ratio of cyclosporin to immunoglobulin therapy is 0.45:1.43 (Papp *et al.*, 2018). Clinicians rather used cyclosporin therapy instead of corticosteroid since the later medication were observed to cause many complications (Chen *et al.*, 2017). Patients were observed to need a shorter duration of hospitalisation stay when treated with cyclosporin (17 days) compared to steroid (26 days) and immunoglobulin (24 days) (Chen *et al.*, 2017).

Other than corticosteroid and cyclosporin A, intravenous immunoglobulin (IVIG) has been known as common treatment to manage SJS/TEN (Kumar *et al.*, 2018). The most acceptable dose is 2g/kg (Kumar *et al.*, 2018). Different study proposed administered 400 mg/kg per day for 5 days is acceptable for SJS/TEN patients (Aihara *et al.*, 2018). The mechanism is mediated through the antibodies inhibition that can prevent apoptosis from occurred (Papp *et al.*, 2018). IVIG can be used alone or combination with other drugs like steroids but low doses of IVIG is sufficient to produce therapeutic effects (Kumar *et al.*, 2018). Beneficial effect from combination of IVIG and steroids is improved compared to the effects promoted by IVIG alone (Aihara *et al.*, 2018). The combinations are found to be restricted only to TEN patient and Asian populations. In TEN patients, mortality rate is reduced by 32%. The mortality rate in Asian populations and non-Asian population are reduce by 22% and 6% respectively (Ye *et al.*, 2016).

Recent study demonstrated improvement in a patient Phenytoin-induced SJS/TEN condition within 48 hours after giving oral tacrolimus 0.12 mg/kg/day. It shared similar mechanism of action like cyclosporin, but larger group studies are needed (Kumar *et al.*, 2018). Plasmapheresis is considered as the first line therapy in comparison to glucocorticosteroid or IVIG where it is effective in shorten during of hospitalisation stay as well as reducing mortality cases (Han *et al.*, 2017). Combination of these therapy with glucorticosteroid or IVIG may not beneficial but need other studies to confirm the results (Han *et al.*, 2017). Other agents like anti- Tumour Necrotic Factor (anti-TNF) have shown its

efficacy in treating TEN by using Infliximab especially in those having greater body surface area detachment. Faster skin-healing process and lower incidence of gastrointestinal compared to systemic corticosteroid. Further research is needed to identify anti-TNF suitable regimen as well as its contraindication (Zhang *et al.*, 2020). Administration 300 mg per day of Cyclophosphamide also an effective approach to treat TEN but the doses need to be tapered to 100 mg per day for up to 6 days (Kumar *et al.*, 2018). Management and treatments involving HLA genotype associated with antiepileptics-induced SJS/TEN includes genetic testing and withdrawal of suspected drug.

Several studies revealed these diseases are related to certain genotype where the actual mechanism remains questionable. Normally, the interactions among the gene variances together with immunological reactions and drug metabolites are thought to be complex. This report will highlight the HLA alleles and its association with Carbamazepine or Phenytoin-inducing SJS/TEN and at the same time summarise the importance of understanding the association of HLA alleles with antiepileptic (Carbamazepine and Phenytoin) and treatments to prevent SJS/TEN, including strategies Malaysia took and practice while handling adverse drug reactions.

II. TYPE B HYPERSENSITIVITY

Type B hypersensitivity is believed to be mediated by immune or inflammatory response. In general, the antigen is taken up by an antigen-presenting cell (APC) then presented to the HLA allele on the MHC complex of T-cell receptors which then help to trigger the production of antibodies. Type B can be further classified into four subtypes which are type I, II, III and IV (Dispenza, 2019). Type I is an immediate hypersensitivity where antibody-mediated Ig that are produced would bound to receptors that can instigate anaphylaxis reactions. Cytotoxic reactions or Type II reactions involve antibodies that are deposited within specific organs which then lead to tissue destruction. Antigen-antibody reactions or immune-complex mediated are known as type III mechanism. Type IV or delayed reactions are the only hypersensitivity mechanism that involves T-lymphocytes rather than antibodies. Steven Johnson Syndrome (SJS) or Toxic Epidermal Necrolysis (TEN) falls under Type IV which involving the activation of CD8+ T cell that leads to apoptosis (Dispenza, 2019).

Drugs or reactive metabolites are able to activate immune response through T cell recognition which can be explained by some theories. The theories include 1) the hapten/prohapten theory, 2) the pharmacological interaction (p.i) concept, 3) the “altered repertoire” model, 4) the “altered t-cell receptor (TCR) repertoire” model, and 5) the danger hypothesis (Fricke-Galindo *et al.*, 2017). Drugs or immunologic metabolites can bind to HLA molecules or repertoire. The first and second theories demonstrated the covalently or noncovalently binding of drugs to the HLA molecules. In “altered repertoire” and “altered t-cell receptor (TCR) repertoire” models, HLA and the TCR will undergo conformational changes once the drug or peptide binds to the self-peptide repertoire or to the receptor. The danger hypothesis explains endogenous cellular alarm signals for example cytokines resulted from the injured cell able to trigger the response. Regardless of what mechanism involved, it can trigger an immune response (Fricke-Galindo *et al.*, 2017).

The pathophysiology of these disease is still a major concern until today because the exact pathophysiology is still unknown (Hasegawa & Abe, 2020). Theoretically, pharmacological interaction (p.i) concept can be used to explain the mechanisms of both diseases (Fricke-Galindo *et al.*, 2017). However, some believe the mechanism is not only limited to pharmacological interaction concept but can also happen through hapten and the altered peptide repertoire model (Yip & Pirmohamed, 2017).

Exposure to trigger medication is considered as the major causes of induction to these diseases where it accounts for 50% to 95% of cases but the frequency may vary each population that is being observed (Fukasawa *et al.*, 2021). At least 100 to 200 drugs are identified as the causes of the SJS or TEN and the common aromatic antiepileptics involved are Carbamazepine and

Phenytoin. The drugs contribute 17% and 9% respectively to the SJS/TEN cases (Dean, 2012). It is important to highlight that aromatic antiepileptics give more effects compared to non-aromatic antiepileptic. A study suggested the presence of the ring structure is responsible for the higher risk of the hypersensitivity reactions (Barbarino *et al.*, 2015). Generally, both drugs are antiepileptics that worked by affecting the ions (sodium, calcium and chloride) channels in the cell membrane that may result in decreasing the excitation or stimulating the inhibition. The drugs also act on preventing the chemical neurotransmitters (GABA and Glutamate) from being transmitted along the synapse. These may affect the electrical and chemical activity of the neurons from reaching the brain (Rogawski *et al.*, 2016). Many adverse effects for drugs are believed to have strong relationship with a person's genetic background (Rogawski *et al.*, 2016). It may be due to a certain HLA serotype that can only be observed in some population (Yuliwulandari *et al.*, 2017).

A. Carbamazepine Hypersensitivity

Carbamazepine (CBZ) is one of the controversial antiepileptics. From 2006 to 2016 reported by China National Knowledge Infrastructure and Wanfang database reported 17.5% cases of adverse reaction relating to the drug (Yang *et al.*, 2018). The drug's active metabolite, CBZ 10,11-epoxide, is produced by the extensive liver CYP3A4 metabolisation of CBZ. Microsomal epoxide hydrolase (mEH), which is encoded by the EPHX gene, converts CBZ 10,11-epoxide into the inactive metabolite CBZ-10,11-diol. Although the rs1051740 of EPHX1 could affect the mEH activity and CBZ and CBZ 10,11-epoxide plasma concentrations (Nakkam *et al.*, 2022). It has been predicted that both SJS and TEN might be linked to the commonly reported HLA alleles especially HLA-B*15:02, HLA-A*31:01 and HLA-B*15:11 (Ahmed *et al.*, 2021). The suspected alleles and Carbamazepine-induced SJS/TEN in different population are summarised in Table 1.

*1. HLA-B*15:02 allele*

The most common HLA alleles associated with ADRs is HLA-B* 15:02 (Ahmed *et al.*, 2021). It was reported that this allele is common among Asian population. The highest cases were reported among the Han Chinese where almost 100% of the 44 patients with SJS/TEN were a carrier for the HLA-B*15:02 Dean, 2012). In Malaysia, association of HLA-B*15:02 predominate among Malay population with 87.5% cases in HLA-B*15:02 carrier followed by Chinese and Indian population with 66.7% and 33.3% respectively (Loo *et al.*, 2018).

However, further studies in other countries such as Japan and Korean showed a lowered HLA-B*15:02 allele frequency (Lerch *et al.*, 2018). It only accounts for less than 1% of the population (Dean, 2012). The data showed that not all Asian countries have the imilar higher frequency of the allele as the Han populations. Among the Caucasians, there is no correlation between these alleles and Carbamazepine-induced SJS/TEN (Yip & Pirmohamed, 2017). This is because only 0.06% of the populations carry the HLA-B*15:02 alleles (Khosama *et al.*, 2017).

*2. Other HLA-B*15 alleles*

Other alleles such as HLA-B*15:11 were reported among Japanese and Korean population (Dean, 2012). A study was made among the HLA-B*15:11 positive in Korean populations showed only three out of seven participant experience SJS when prescribed with Carbamazepine. However, in Central China population demonstrate that the risk of getting SJS is high among HLA-B*15:02 negative (Cheng, 2021). Among Japanese population, the prevalence of these diseases is lower where only four people experience these diseases when given Carbamazepine even though the rest of the participant also HLA-B*15:11 positive (Dean, 2012). Despite all the existence alleles induced SJS or TEN, only HLA-B*15:02 positive individuals are susceptible to experience SJS or TEN (Lerch *et al.*, 2018). Recently studies reported, people with CBZ-induced SJS/TEN did not show the presence of the HLA-B*15:02 allele but showed the

presence of the HLA-B*15:21 and HLA-B*15:11 alleles. HLA-B*15:21 and HLA-B*15:11 alleles belong to the HLA-B75 serotype, which consists of the HLA-B*15:02 allele as well. The HLA-B75 serotype may encode proteins with a similar conformation for CBZ binding and presentation, triggering the immune response associated with CBZ-induced SJS (Nakkam *et al*., 2022). *HLA-A*24:07* allele may be used as a biomarker to predict susceptibility to carbamazepine-induced SJS/TEN in Filipino patients in the recent study (Capule *et al*., 2021).

*3. HLA-A*31:01 allele*

A study reported that HLA-A*31:01 is responsible for the adverse reactions among the European (Khosama *et al*., 2017). In North Europeans result showed that 5 participants showed the reactions in the total of 12 participant (McCormack *et al*., 2011). This allele also been identified in Japanese population however, prevalence (9%) is higher compared to the North European population (2 to 5%) (Mushinoda *et al*., 2018). In Malaysia, 50% cases reported among Indian population who carried HLA-A*31:01 alleles compare to Malay and Chinese population with zero cases reported (Yip & Pirmohamed, 2017).

B. Phenytoin Hypersensitivity

Phenytoin (PHT) is also been classified as high-risk drugs that can induce TEN by some researchers [34]. It also can be considered as aromatic drugs that have similar structure to Carbamazepine. One of the primary enzymes involved in the metabolism of phenytoin is CYP2C9, and different CYP2C9 alleles have been shown to affect the drug levels of phenytoin. People with CYP2C9 variants with decreased activity may have slower rates of phenytoin clearance and are more likely to experience dose-related side effects (Dean & Kane 2016). A study in China demonstrated less than 1% cases were reported involve the use of Phenytoin (Yang *et al*., 2018).

*1. HLA-B*15:02 alleles*

HLA-B*15:02 also been demonstrated the major causes to induce Phenytoin-SJS/TEN that account almost 30.8% cases (Cheng, 2021). In Malaysia, more than 60% cases show strong association between HLA-B*15:02 and Phenytoin (Chang *et al*., 2017). Nevertheless, another study in Thai children showed different result where this allele did not induce any cutaneous adverse reaction (Chouchiet *et al*., 2018). Similar to the study been done among European and Japanese where the frequency is lowered (Cheng, 2021).

2. Other HLA-B 15 alleles*

For the Malay population, HLA-B*15:13 allele is responsible for the Phenytoin-induced SJS/TEN where 13 patient experience SJS/TEN in a total of 348 subjects (Chang *et al*., 2017). Compared to Carbamazepine-induced SJS/TEN, this allele had been reported to have no association in Phenytoin–SJS/TEN patients with Caucasian, African or Japanese genetic backgrounds (Cheng, 2021). However, HLA-B*15:02 is strongly associated in Carbamazepine-inducing SJS/TEN compared to Phenytoin-inducing SJS/TEN (Dean, 2012). The summary of HLA alleles association with Carbamazepine or Phenytoin-induced SJS/TEN are summarised in Table 1. It has been reported by several studies that other alleles such as HLA-A*57:01, HLA-A*02:06, HLA-A-A*24:02, HLA-DRB1*04:05 and HLA-C*08:01 also can induce SJS/TEN (Fricke-Galindo *et al*., 2017). The summary of the occurrence of these alleles in different populations is summarised in Table 2.

Table 1. HLA alleles association with Carbamazepine or Phenytoin-induced SJS/TEN

Drugs	HLA Alleles	Population	References
Carbamazepine	HLA-B* 15:02	Han Chinese	Strong association is reported in various studies (Couchi *et al*., 2018)
		Malaysia	Malay population is predominated with induced SJS/TEN compared to Chinese and Indian (Khor *et al*., 2017)
		Caucasian	Little or no association is reported due to low allele frequency (Dean, 2012)
		Asian population	Only small percentage of HLA-B*15:02 positive people experienced SJS/TEN in Korean and Japanese population (Chang *et al*., 2017)
	HLA-A*31:01	North European	-In different study, this allele rather causes maculopapular exanthema (MPE) or drug rash with eosinophilia and systemic symptoms (DRESSS) rather than SJS/TEN among European (White *et al*., 2018)
		Japanese	-HLA-A*31:01 allele is also believed to induce any cutaneous adverse drug reactions among the Japanese descent (Mushinoda *et al*., 2018)
		Malaysia	Only observed among Indian population with no frequency reported among Chinese and Malay (Khor *et al*., 2017)
	HLA-B*15:11	Korean Japanese	Allele frequency is less than 1 with 0.0088 and 0.0166 respectively (Ahmad *et al*., 2021)
Phenytoin	HLA-B*15:02	Han Chinese Thailand	Limited evidence to show the involvement of these allele in causing hypersensitivity when using Phenytoin. Studies only focus on Carbamazepine (Dean & Kane, 2016)
		Malaysia	At least 61.5% subjected experience SJS/TEN using Phenytoin therapy but does not showed other type of hypersensitivity such as drug rashes with eosinophilia systemic symptoms (DRESS) (Ahmad *et al*., 2021; Chouchi *et al*., 2018)
	HLA-B*15:13	Malaysia	HLA-B*15:13 is ethnicity-specific marker with the highest frequency is showed in Malay (Cheng *et al*., 2017)
		Thailand Han Chinese	Both populations have lower allele frequency compared to Malay with 0.1% to 0.3% and 1.8% respectively (Cheng *et al*., 2017)

Table 2. Other alleles associated with Carbamazepine or Phenytoin-inducing SJS/TEN

Other Alleles	Association
HLA-A*57:01	Recent data from Allele Frequency Net Database, HLA-A*57:01 is dominant among the population with the frequency of 2.5% to 8.9% but the interaction of this HLA genotype and Carbamazepine need further exploration (White *et al*., 2018)
HLA-A*24:02	Carbamazepine and Phenytoin are reportedly to cause these hypersensitivity reactions in HLA-A*24:02 patients. In similar study, HLA-A 24:02 is seen to be correlated to higher prevalence to induce Carbamazepine-SJS/TEN among the HLA-B*15:02 negative (Wang *et al*., 2019)
HLA-C*08:01	Interestingly, for HLA-C alleles, only one study has shown any observation related to it, where HLA-C*08:01 is observed to induce SJS/TEN on eight patients when initiated with carbamazepine (Chen *et al*., 2006)
HLA-DRB1*04:05	Weaker association of HLA-DRB1*04:05 and Carbamazepine-induced SJS/TEN was also found in similar study where only 41 patients experienced SJS/TEN from a total of 60 people (Chen *et al*., 2006)

3. Other drugs hypersensitivity

Other drugs such as Allopurinol was also reported as high-risk medications that can induce skin reactions among Asian and European (Cheng, 2021). However, greater fold risks are identified among the Han Chinese with highest odd ratio (OR) (229.7, 127.60 and 203.40) and Thailand (348.3) to the lesser extend among the Korean (97.8), Japanese (40.83) and European (Cheng, 2021; Wang *et al*., 2022). One study from Australia discussed the allopurinol-inducing SJS/TEN (Wang *et al*., 2017). The study reported that HLA-B*58:01 is the strong predictor in emergence SJS/TEN involving this gout medication. Other HLA-B genotype such B*59:01, B*38 and B*73:01 responsible for the SJS/TEN incidences involving Methazolamide, Oxicam and Sulphamethoxazole (Wang *et al*., 2017).

Overall, HLA-B*15:02 and T-cell receptor clonotype involvement are believed to mediate the pathophysiology for both SJS and TEN (Sousa-Pinto *et al.*, 2016). Several studies already proven that antiepileptics can activate immune reaction through several pathways (Fricke-Galindo *et al.*, 2017). Hypersensitivity resulted from the generation of chemically modified protein which previously undergo protein serum modifications by carbamazepine reactive metabolites through hapten theory (Fricke-Galindo *et al.*, 2017). Through PI interaction, Carbamazepine can directly bind to the HLA-B*15:02 which located between the *HLA-B*15:02*/peptide and T-cell receptor (Fricke-Galindo *et al.*, 2017). Once bind to CD8+ T cell, cytokines such as perforin, Fas-Fas Ligand, TNF alpha and granulysin will be secreted that could make keratinocyte to undergo apoptosis that explain the pathogenesis of SJS/TEN (Mautaouakkil *et al.*, 2018). In last mechanism, Carbamazepine binding to *HLA B*15:02* could cause the self- repertoire to undergo alteration which lead to T cells activation (Lerch *et al.*, 2018).

Genetic predisposition could expose individual to SJS/TEN (Li *et al.*, 2015). As mentioned, drugs cause hypersensitivity reactions relate to HLA genotype but most drugs still cannot identify the actual HLA association (White *et al.*, 2018). In fact, at least 20 % case involving SJS/TEN not yet identify the culprit drug (White *et al.*, 2018). Other than HLA genotypes, CYP 450 variance also a part of genetic factors that could influence people susceptibility to adverse drug reactions. HLA variances involve immunological mechanism while CYP 450 variances involve drug metabolism pathway. CYP2C9 is one of the common CYP 450 families that have plays important role in metabolising (Phenytoin Tassaneeyakul *et al.*, 2016). Delayed in biotransformation process increase the risk of having SJS/TEN especially in those who carry CYP2C9*3 (Osama, 2016). Non-genetic factors such as patient status, co-medications and medical therapy treatment are some non-genetic that could also contribute the SJS/TEN. Currently, no evidence from any study to support the hypothesis since no study has been done to prove such non-genetic factors could lead to hypersensitivity reactions (Yampayan *et al.*, 2017).

In other study, stated that HLA-B*44:03 may be associated with lamotrigine-induced SJS/TEN among Koreans. Lamotrigine is used to treat epilepsy, including focal seizures, tonic–clonic seizures, and seizures in Lennox–Gastaut syndrome, and to prevent the recurrence of depressive–manic episodes in patients with bipolar disorder (Dashti *et al.*, 2022). Abacavir is effectively for treatment with HIV infection, and it has been reported that hypersensitivity reactions induced by abacavir is strongly associated with HLA-B*57:01 in Australia's, U.S. and European. HLA-A*02:06 is strongly associated with acetaminophen-related SJS/TEN with severe ocular complications in Japan population (Wang *et al.*, 2022).

III. GENETIC TESTING

Some preventive measures had been taken to prevent the disease such as supportive care, immunoglobulins including the uses of genetic testing (Kumar *et al.*, 2018). Nowadays, people are more aware about the genetic testing since the internet are more accessible and information are shared ever more rapidly. Genetic testing is defined as a test to detect the any abnormalities in human DNA, RNA, chromosomes and proteins that are responsible for the inherited disorder. It can do by some mechanisms which it can directly examine DNA or RNA, observes the gene's markers that related to the emergence of certain diseases, examine the chromosomes and proteins products of the genes. Genetic testing in clinical practices has become as common to conduct as the specific drug or laboratory test based on the patient request (Pagon *et al.*, 2001).

Since the HLA have its own characteristics and features such as homogenous or heterogenous, the choice of testing must be considered as the it determines the specificity of the testing. The HLA-B alleles is highly polymorphic that could make the detection process become so challenging (Fang *et al.*, 2019). Many approaches can be used to detect HLA-B alleles and only four major approaches that are currently available (Fang *et al.*, 2019). The most accurate method is direct

sequencing but it can be expensive, require special expertise and some time is needed to analyse its data (Nguyen *et al*, 2019). Sequence-specific oligonucleotide probe hybridisation (SSOP) also can be used to differentiate HLA class (Fang *et al*., 2019). Next approach is sequence-specific PCR (SSP-PCR) but most laboratory finds it difficult to resolve HLA-B15 family using this method (Fang *et al*., 2019). A study reported that only two-SNP haplotype can be a proxy tagging SNPs for HLA-B*15:02 which are rs2844682 and rs3909184. Recent study proved has shown there is strong association between SNP within HLA-B*15:02 which is the rs144012689 variant (Yampayon *et al*., 2017). Tag SNP method on the other hand, can only be used in HLA typing if any strong linkage disequilibrium is identified between SNP and HLA allele (Dean, 2012). This approach uses different tag SNPs to observed the different HLA variants in different population (Dean, 2012). The most identified tag SNP for HLA-B*15:02 is rs2844682 and rs3909184 (Dean, 2012). In Europe, rs1061235 is identified as potential tag SNP but it is not suitable for non-Caucasian individual [35]. As for Japanese, the possible tag SNP would be rs16333021 (Dean, 2012). A study reported that HLA genotyping cost will be diminished when perform test involving the identification of the specific alleles with the single nucleotide polymorphism in linkage disequilibrium which can also be used for different populations (Chen *et al*., 2014). According to some studies, pharmacogenomic testing for HLA-B*15:02 would be more cost-effective if the prevalence of this allele was greater than 5% or at least 2.5% (Biwas *et al*., 2022).

Among of all the screening assays, the Real-time PCR had been identified as the most suitable strategies in screening the HLA allele (Nguyen *et al*., 2019). In screening HLA-B*15:02 and other allele, various approaches had been used to detect the target alleles. However, majority of the methods have its own limitations. The Loop Mediated-Isothermal Amplification method (LAMP) for example, have a high probability to get false results due to the fact that PCR is an open system. The similar limitations were observed in other different types of methods and studies (Nguyen *et al*., 2019).

HLA-B genotyping has been performed in different population manage to identify the affected alleles that cause the emergence SJS/TEN incidence. The use of genetic testing provides many advantages as it is believed help prevent the mortality and morbidity cases among the Type B reactions in certain population (Osanlou *et al*., 2018). Other studies have also proved significantly reduced the emergence of the SJS and TEN (Nguyen *et al*., 2019). Two studies in Taiwan proved that higher negative predictive value was observed for the HLA-B*15:02 screening and some of the cases had been successful prevent these diseases (Mautaouakkil *et al*., 2019). As for other alleles for example HLA-A*31:01, screening the allele among Japanese population showed positive outcome in preventing SJS or TEN associated with the Carbamazepine in which it prevents 16 SJS or TEN cases in every 118 cases (Mushinoda *et al*., 2018). A study reported that implement Single Nucleotide Polymorphism (SNP) genotyping enable to reduce the risk to develop SJS/TEN from 5% to 3.8%. among the HLA-B*31:01 positive (Mushinoda *et al*., 2018). A study demonstrated implementing HLA genotype screening cause a sudden decrease of Carbamazepine prescribing were reported this may due to increase awareness about antiepileptic that can result in hypersensitivity reactions (Chen *et al*., 2014).

Beside the clinical benefits, the HLA screening also provide various economic benefits which includes cost effectiveness (Nguyen *et al*., 2019). Other advantages include improve patient adherence to medications, discontinuation unnecessary medications and enhance decision making between patient and healthcare professional. Despite all the advantages mentioned, there are some disadvantages as well. Special considerations still need to be followed before considering any testing (Pagon *et al*., 2001). Some of the considerations involved personal decision making and time consuming, longer time taking to obtained the result may lead to sudden AED prescribing by the clinicians which increase the expenditure without actually gaining benefits from it. Thus, patient still

subjected to other additional consultation review. Furthermore, the therapy can only be called effective if the allele prevalence is higher than 2.5% (Nguyen *et al.*, 2019). A study found out that extending the Phenytoin screening is not suggested as it will only increase the expenditure since only 0.65% cases involving Phenytoin -inducing SJS/TEN (Chen *et al.*, 2016). Phenytoin and Carbamazepine are structurally similar but, the genetic association of HLA-B*15: 02 in phenytoin-induced SJS/TEN still cannot be clinically valuable compared to carbamazepine (Hung *et al.*, 2010). Among the Singaporean Indian for example, initiating HLA-B* 15:02 genetic testing prior to Carbamazepine therapy is considered non-cost effective due to the extremely rare occurrence of the genetic markers in individual of Indian descent (Chen *et al.*, 2016; Dong *et al.*, 2012). Poor adherence to the policy, shifting to other antiepileptic drugs as an alternative option for Carbamazepine which lead SJS/TEN subsequently increase the cost expenditure (Shanbhag *et al.*, 2021).

IV. MEDICATION WARNING LABEL

Similar recommendations have been be seen for Phenytoin-induced SJS/TEN cases, there are not to be prescribed among HLA-B*51:02 positive (Dean & Kane, 2016; Tsukagoshi *et al.*, 2021). Even though phenytoin is an alternative drug for Carbamazepine, it cannot be used among the HLA-B*15:02 positive. Other countries such as Canada, Japan and Australia have include pharmacogenetic information into their drug label as summarised in Table 4.

Table 3. Advantages and disadvantages of genetic testing

Characteristic	Advantages	Disadvantages
Clinical benefits	Effective in reducing incidence rate.	Only be done in certain population.
Economic benefits	Proven to be cost-effective by various studies. Effective in diagnosing a newly diagnosed epilepsy patient involving HLA-B*31:02.	Only effective in large group of HLA-B subject.

V. RECOMMENDATIONS

Established international agencies are already providing solutions in regarding to the HLA-antiepileptic association. According to the US Food Drug Administrations (FDA), genetic testing involving the use of Carbamazepine in regard to HLA-B*15:02 induced SJS/TEN, is best recommended to be done in some populations. Some of the recommendations includes performing screening test among the Asian population before prescribing anti-epileptic drugs (FDA, 2019). It is also compulsory to avoid Carbamazepine in any drug therapy unless the benefit exceed the risk among HLA-B*15:02 positive individuals. As for HLA-*B 31:01 positive, it is necessary to identify the risks and benefits before initiating Carbamazepine therapy. In addition, recommendation from Dutch Pharmacogenetic Working Group (DPWG) guideline also can be considered in HLA-B *15:02, -B* 15:11 and -B*31:01 positive where alternative option can be initiated (Dean, 2012; Wang *et al.*, 2019).

Clinical Pharmacogenetic Implementations Consortium (CPIC), has a broad recommendation which is specific for HLA-B* positive or negative. For people who are negative for both alleles of HLA-B*15:02 and HLA-B*31:01, normal Carbamazepine dosing can continue on the normal medication. Similar recommendation from FDA and DPWG for the HLA-B*15:02 positive where Carbamazepine should be changed to an alternative prescription (Dean, 2012). Nevertheless, it is optional to perform the testing if the patient does not demonstrate any cutaneous adverse reactions following exposure to carbamazepine after three months (Dean, 2012).

A. Approaches by The Malaysian Regulatories

Genetic testing already been use worldwide due to the modern technology. However, in Malaysia, the pharmacogenetics in medical curricula has only been introduced in three main public universities out of the 30 medical schools (Shafie *et al.*, 2020). It is important to introduce the related syllabus into the curricula to create awareness. The main service provides by health professional in relation to genetically linked ADR would be genetic counselling. This is mostly performed by medical geneticists and genetic counsellors. Medical geneticists are important to confirm genetic diagnosis and order genetic testing while genetic counsellors are responsible to provide continuous psychosocial support to patient and reinforce genetic information through genetic education. Recently, it is reported that Malaysia only have less than 10 professional group for genetic counsellors (Zhou *et al.*, 2021). A common initial step in countries that does not have any genetic counsellors is to train their nurses and scientists. In Malaysia, proposing the idea of specialisation as a genetic nurse had been proposed into the nursing professional (Lee & Thong, 2013). Besides, the shortage number of trained geneticists, cost of therapy, outdated technology also become the barrier for the implementation of the pharmacogenetic practices in Malaysia (Qian *et al.*, 2019).

Table 4. Description of pharmacogenomic information in the three drug labels of the Canada, Australia and Japan.

Drugs	**HLA alleles**	**Canada**	**Japan**	**Australia**
Carbamazepine	HLA-B15:02	(Boxed Serious Warning and Precautions) • Found in almost individual with Asian ancestry • HLA-B*15:02 genotyping is recommended at greater risk populations • Use of Carbamazepine or other antiepileptics in those HLA-B15:02 alleles positive is acceptable if further information is available otherwise it still prohibited	(Side Effects/Other Precautions) • Very low allele frequency of HLA-B*15:02 in Japanese population compared to Han Chinese with 0.001 and 0.019 to 0.124 respectively	(Special Warnings and Precautions for Use) • Patient with ancestry in genetically-risk population should consider to underwent testing • Avoid the use of Carbamazepine in patients who had tested positive for HLA-B*15:02 if benefits outweigh the risks
	HLA-A*31:01	(Box Serious Warnings and Precautions) • HLA-A*31:01 genotyping is recommended at greater risk populations • Use of Carbamazepine or other antiepileptics in those HLA-A*31:01 alleles positive is acceptable if further information is available otherwise it still prohibited	(Side Effects/Other Precautions) • Relatively high allele frequency in Japanese with 0.071 to 0.120.	(Special Warnings and Precautions for Use) • Patient with ancestry in genetically-risk population should consider to underwent testing. • Avoid the use of Carbamazepine in patients who had tested positive for HLA-A*31:01 if benefits outweigh the risks

Phenytoin	HLA-B*15:02	(Warnings and Precautions) • Found in almost individual with Asian ancestry • HLA-B*15:02 genotyping is recommended at greater risk populations • Use of Phenytoin or other antiepileptics in those HLA-B15:02 alleles positive is acceptable if further information is available otherwise it still prohibited	(Side Effects) • Severe cutaneous adverse reactions such as TEN and SJS can be seen in epilepsy patient with Phenytoin	(Special Warnings and Precautions for Use) • Risk of developing SJS/TEN in HLA-B*15:02 patient of Asian ancestry taking drug associated with SJS/TEN including Phenytoin • Consider avoiding using drugs that can induce SJS/TEN otherwise alternative therapy is available.

V. CONCLUSION

Although Steven Johnson Syndrome (SJS) and Toxic Epidermal Necrolysis (TEN) are rare diseases but the conditions are life-threatening. Adult and female are largely affected by these diseases and the most common reported medications are antiepileptics (Carbamazepine and Phenytoin). In addition, Asian decedents from countries such as China, Korea, Japan, Thailand and Malaysia are seen to have higher incidence of SJS/TEN compared to ethnicities of other countries. Genetic predisposition like HLA-B*15 subgroup is the important genotype that is directly linked to SJS/TEN. Nevertheless, higher allele frequencies are observed in Asian population compare to Caucasian, Korean and Japanese. Conclusively, HLA-B*15:02 is an ethnicity- and phenotype -specific marker. Together with suspected alleles and antiepileptics (CBZ and PHT) a person can have a greater risk of experiencing both diseases rather than those people who do not carry any of the candidate alleles. Hence, pharmacogenetic testing is important to be implemented in clinical practice before start prescribing both antiepileptic to avoid such reactions. Once the alleles are identified, decision to withdraw culprit drugs and switching to alternative medication can be made in accordance to each establish agencies' recommendations.

The use of HLA screening depends on three important elements. First, the medications that are suspected to cause the SJS/TEN must be commonly used and act as first-line therapy, and expensive. Next, the high prevalence of carriers of risk allele should be observed in the screening populations. Last, the cost to perform this screening test must be minimised to promote more involvement from various populations.

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