UNIVERSITI TEKNOLOGI MARA

RELEVANCE OF GENETIC POLYMORPHISM OF *HLA-B*1502* IN CARBAMAZEPINE-INDUCED CUTANEOUS ADVERSE DRUG REACTIONS

HASBULLANI BIN ZAKARIA

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AUTHOR'S DECLARATION

I declare that the work in this thesis was carried out in accordance with the regulations of Universiti Teknologi MARA. It is original and the result of my own work, unless otherwise indicated or acknowledged as referenced work. This thesis has not been submitted to any other academic or non-academic institution for any other degree or qualification.

I, hereby acknowledge that I have been supplied with the Academic Rules and Regulations for Postgraduate, Universiti Teknologi MARA, regulating the conduct of my study and research.

Name of Student	: Hasbullani bin Zakaria
Student I.D. No.	: 2011277286
Programme	: Master of Science
Faculty	: Faculty of Pharmacy
Thesis Title	: Relevance of Genetic Polymorphisms of *HLA-B*1502* in Carbamazepine-induced Cutaneous Adverse Drug Reactions
Signature of Student	: .....
Date	: October 2014

ABSTRACT

Adverse drug reaction (ADR), commonly termed as unwanted reaction is a long-standing and a major medical problem that comes with many clinically important drugs. ADRs are broadly categorized into predictable (type A) and unpredictable (type B) reactions. Predictable reaction is usually dose dependent, related to the known pharmacologic actions of drugs, and occurs in healthy individuals. Unpredictable reactions are generally dose independent, are not related to the pharmacologic actions of drugs, and only occur in susceptible individuals. Stevens Johnson Syndrome (SJS) and Toxic Epidermal Necrolysis (TEN) are two fatal ADR encountered in some patients prescribed carbamazepine or phenytoin. US FDA had published a medical alert with a recommendation of *HLA-B*1502* screening before these two (2) drugs were prescribed to patients with Asian ancestry as the likelihood of SJS/TEN were highly associated with *HLA-B*1502.* For the methods, eighty (80) healthy unrelated individuals and eighty six (86) patients attending clinics at Department of Neurology of a local hospital were recruited. DNA was extracted from blood samples obtained from each patient. *HLA-B*1502* genotype was determined by AS-PCR developed in house. All statistical analysis was performed using SPSS software version 20. *P* values ≤ 0.05 were considered statistically significant. The strength of association between *HLA-B*1502* with CBZ-induced SJS-TEN was estimated by calculating the odd ratio. For the results, among the 86 patients, 40 were newly registered patients and genotype screening was conducted before patients were prescribed with CBZ. Among this group, 17.5% were positive for *HLA-B*1502.* In another cohort in which CBZ had been withdrawn due to SJS/ TEN; all of them (15) were positive for *HLA-B*1502.* One patient with positive *HLA-B*1502* however did not develop SJS/TEN and is therefore tolerant. The frequency of *HLA-B*1502* allele in CBZ-SJS/TEN after CBZ prescribed was 32.6%. The calculated ratio of patients at risk of developing SJS/TEN based on this small samples size is 120.2727 (95% CI : 6.1202 – 2363.5775; $p = 0.0016$). For the conclusion, the screening of patients for the *HLA-B*1502* allele before the initiation of carbamazepine treatment and withholding carbamazepine from *HLA-B*1502*–positive patients can reduce the incidence of carbamazepine-induced SJS-TEN among the Malaysia. This study conclude that the implementation of *HLA-B*1502* screening is necessary to avoid patients at risk of SJS/TEN from being prescribed CBZ due to the high odd ratio observed in this study.

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