UNIVERSITI TEKNOLOGI MARA

THE RELEVANCE OF *HLA-B*5801* PHARMACOGENOTYPING IN PERSONALISING ALLOPURINOL THERAPY

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ABSTRACT

Allopurinol is one of the drug reported to cause cutaneous ADR. From previous studies, Allopurinol causing SCAR was strongly associated with *HLA-B*58:01* in Han Chinese population. The allele was present in all patients with allopurinol induced SCAR (51 out 51) but only 15% (20 of 135) in allopurinol tolerant patient and 20% (19 out 93) in the general population. The odds ratio (OR) to a patient with allopurinol induced SCAR was significantly high, 580.0 with a *p* value of $4.7x10^{-24}$ (Hung *et al,* 2005). This association was also observed in Thai population (Tassaneeyakul *et al*, 2009) and Korean population (Kang *et al*, 2011). This study to determine the association between *HLA-B*58:01* and clinical association of Allopurinol induced cutaneous adverse drug reaction in Malaysian population. As a conclusion, AS-PCR for the simultaneous detection of *HLA-B*58:01* allele was successfully developed. This method provided a more rapid and convenient way in detection of single nucleotide polymorphism. We also have successfully genotyped our patients. The interesting finding in this study would be able to provide a preliminary data of *HLA-B*58:01* allele and genotype in patients who experienced SCAR after allopurinol initiation. Based on the results, *HLA-B*58:01* allele is significantly associated with the increased risk of SCAR in patients using allopurinol. Therefore, this study recommended the pharmacogenetic test of *HLA–B*58:01* may provide personalized medicine in clinical application and a valid marker to prevent allopurinol induced serious cutaneous reactions.

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CHAPTER ONE

INTRODUCTION

1.1 BACKGROUND

Adverse drug reaction (ADR) as defined by World Health Organization (WHO) is a response to a drug which is noxious and unintended, and which occurs at doses normally used in manfor prophylaxis, diagnosis, or therapy ofa disease or for the modification of physiological function (Edwards and Aronson, 2000). Some of these reactions are known side effects of the drugs but sometimes it can be new and unrecognized reactions (Reporting Adverse Drug Reactions, BMA Board). The most common adverse drug reactions (ADR) were the cutaneous adverse reactions. These reactions range from mild to severe and life-threatening as in the case of drug-induced hypersensitivity syndrome (DIHS), Stevens-Johnson syndrome (SJS) and Toxic Epidermal Necrolysis (TEN). These severe and life threatening cutaneous reactions are known as severe cutaneous adverse reactions (SCAR).

SCAR is variable in both mechanism and clinical features. Most often SCAR is immune mediated, unpredictable and not dose dependent. Human leukocyte antigens (HLA) which present antigen (8-18 peptide residues) to the T-cell receptor (TCR) have been associated with ADR related to immune response. It has been indicated that this mechanism is involved in the pathogenesis of SCAR (Chung *et al.,* 2007).

Recent evidence supports that variations of human leukocyte antigens (HLA) genotype become a major susceptible factor predisposing individuals to develop hypersensitivity immune mediated reaction (Chung *et al.,* 2007). HLA is located at the major histocompatibility complex (MHC) region on human chromosome 6p.21.3. It plays a central role in the immune reaction bypresentingantigen to the T-cell receptor (TCR). In the presence of a proper co-stimulatory molecule, HLA antigen–TCR complex will form a synapse which elicits an immune response with memory characteristic (Chung *et al.,* 2007).

Allopurinol is one of the drugs reported to cause SCAR. From previous studies, SCAR caused by allopurinol was strongly associated with *HLA-B*58:01* in Han Chinese population (Hung *et al.,* 2005). The allele was present in all patients with allopurinol induced SCAR (51 out 51) but only 15% (20 of 135) in allopurinol