

UNIVERSITI TEKNOLOGI MARA

**THE INFLUENCE OF GENETIC
POLYMORPHISMS OF CYP3A ON
THE PHARMACOKINETIC
VARIATION AND CLINICAL
OUTCOMES OF TACROLIMUS IN A
COHORT OF PATIENTS**

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Thesis submitted in fulfillment
of the requirements for the degree of
Master of Science

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AUTHOR'S DECLARATION

I declare that the work in this thesis was carried out in accordance with the regulations of University 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.

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ABSTRACT

The complexity of determining the variability in tacrolimus pharmacokinetics parameter among organ transplant patients and its narrow therapeutic window characteristics necessitates proper drug monitoring in order to ensure the level is maintained within therapeutic range. Many studies have reported that variability of tacrolimus pharmacokinetics was due to differential expression of drug metabolizing enzymes CYP3A4 and CYP3A5 encoded by *CYP3A4* and *CYP3A5* genes respectively. The aim of the study was to develop a genotyping method in detecting *CYP3A4*18*, *CYP3A5*3* and *CYP3A5*6* mutations as well as investigating any correlation of genotyping findings with the clinical and tacrolimus related pharmacokinetics data and to quantify enzyme expression through the relationship of *CYP3A4* and *CYP3A5* mRNA copy number with the patients' genotypes. Five ml of blood were withdrawn from the 80 patients and the DNA was extracted, thus proceeded for genotyping of *CYP3A4*18*, *CYP3A5*3* and *CYP3A5*6* variants using two steps PCR technique. Absolute quantification was employed where the serial dilution of plasmid from cloned bacteria to generate a standard curve was done prior to real time PCR method. Nine of 80 patients were found to be heterozygous of *CYP3A4*18* (11.25%). As result of *CYP3A5*3* polymorphism, eight patients were found as homozygous wild type (10%), 31 patients were heterozygous (38.75%) and 41 patients were homozygous mutant (51.25%). No *CYP3A5*6* mutation was observed in this study. Homozygous mutant was significantly associated with lowest requirement of tacrolimus dose and highest adjusted level per dose ($P < 0.01$). There was no significant correlation between *CYP3A4* and *CYP3A5* mRNA copy number with the *CYP3A4*18* and *CYP3A5*3* genotypes respectively. Significant correlation between *CYP3A5*3* genotypes with the doses has provided a reliable information in predicting the appropriate individual tacrolimus doses.

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