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Title : **Variability In Responses Of Tacrolimus In Kidney Transplant Patients: The Use Of Pharmacogenetics And Metabolomics In Closing The Gaps In Clinical Practices**

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Kidney transplantation is widely accepted to be the best option for patients with end-stage kidney disease. After transplantation patients would be maintained on immunosuppressive agents to lower the activity of their immune system and vigilant surveillance is important to monitor other post-transplant complications. Tacrolimus (FK506) is a calcineurin inhibitor that has been widely used as an immunosuppressive agent in patients undergoing organ transplantation. However, its clinical use is complicated due to its narrow therapeutic window and wide interindividual variation of responses to immunosuppressive therapy. Therefore,

it remains a challenge for clinicians to optimize the immunosuppressive drug to minimize the risk of rejection and at the same time avoid toxicity despite conventional therapeutic drug monitoring (TDM) being performed. In addition, the determination of toxicity and rejection still solely depend on the invasive procedure of biopsy. Thus, this study aims to investigate the impact of pharmacogenomics and metabolomics in monitoring the efficacy of tacrolimusand other post-transplant complications. A total of 282 healthy controls and 80 kidney transplant patients treated with tacrolimus from three major ethnic groups (Malay, Chinese and Indians) were recruited. Blood and serum samples were collected to obtain DNA, RNA and metabolites and clinical data of the patients were also collected. For patients and healthy controls samples, the distribution of three *ABCB1* SNPs were investigated (*C1236T, G2677T/A* and *C3435T*) and were found to be in high frequency as being reported by other Asian population. However no correlation was observed between these SNPs and clinical outcomes. Exploration of *CYP3A5 A6986G* distribution among patients reveals that the frequency of variant allele (*CYP3A5*3*) to be in high frequency. The homozygous variant genotype (*CYP3A5* non-expressor) was significantly correlated with low dose requirement but high level of dose-adjusted ratio for tacrolimus. This genotype was also found to be significantly high among Chinese patients who exhibited similar trend of tacrolimus dose and dose-adjusted ratio. Absolute quantification of *ABCB1* blood mRNA level using quantative PCR (qPCR) reveals that the expression level was heterogenous although the variation cannot be explained by the *C1236T, G2677T/A, C3435T* or the haplotypes. However, a significant inverse correlation was demonstrated between *ABCB1* mRNA level and tacrolimus doseadjusted ratio that highlights the need for the search of other causal variants for *ABCB1*. Global metabolite profiling using Quadrupole Time-of-Flight (Q-TOF) LC/MS platform of patients and healthy controls' sera as well as patients with other criteria demonstrated plenty of compounds that were in different abundance. A total of 9 groups of compound were found to have potential to be developed into biomarkers. However, all of these potential compounds need to be further validated before being introduced into clinical setting. This pilot study demonstrates the potential of integration between pharmacogenomics and metabolomics to complement conventional therapeutic drug monitoring practice and to assist physicians in achieving the target of personalized medicine.