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Abstract Title:- Effect of Human Leucocyte Antigen Genotypes on Tacrolimus Pharmacokinetics in Renal Transplant Patients

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Aims:-To study the association of Human Leucocyte Antigen alleles, haplotypes, haplotype combinations and genotypes with Tacrolimus Concentration by dose ratio (Co/D).

Methods:- 411 renal transplant patients were enrolled in the study. Average and standard deviation were used for summarization of quantifiable parameters. Frequency distribution of various HLA-A, B, C, DRB1, DQB and DQA Locus Alleles, Haplotype, Haplotype combination and genotype with tacrolimus Co/D at five different time points 7th day, one month, three months, six months, and one year of post-transplantation was obtained using Descriptive analysis in SPSS Software. Association of HLA alleles, haplotypes, haplotype combinations and genotypes with Tacrolimus Co/D was performed using one-way ANOVA Multiple comparisons using Least Significant Difference method. The univariate linear model analysis was carried out to find the most significantly associated HLA out of the significant HLA obtained from LSD analysis.

Results:- Of 411 patients, 345 (83.94%) were males and 66 (16.06%) were females. In the majority of patients, Native Kidney Disease (NKD) had Undetermined causes [145(35.28%)] followed by Diabetes mellitus nephropathy [39(9.49%)], Chronic glomerulonephritis [33(8.03%)] and Immunoglobulin A Nephropathy [18(4.38%)]. Most patients were found with comorbidity Hypertension (252(61.31%)) and Anemia [162(39.42%)] followed by Metabolic bone disorder [79(19.22%)] and Diabetes Mellitus [32(7.79%)]. A total of 21 HLA, including 5 alleles, 5 haplotypes, 5 haplotype combinations and 6 genotypes, were found to be significantly associated with Tacrolimus Co/D by using One-way ANOVA post-Hoc Least Significant Difference (LSD) analysis. Finally, 3 HLA, including allele A* 33, haplotype A*33:01 and A*02:06, were found to be highly significantly associated with Tacrolimus Co/D by Univariate linear model analysis out of the significant HLA obtained from LSD analysis.

Conclusions:- Allele A* 33, Haplotype A*33:01 and A*02:06 were found to be significantly associated with Tacrolimus Co/D. The Average Co/D was observed to be high at all time points in patients with these HLA, suggesting that it might cause Tacrolimus-induced toxicity in future. This suggests that lower dose should be given to the patients with these HLA.

Keywords:- Tacrolimus, Pharmacokinetics, Pharmacogenomics, Human Leucocyte Antigen, Renal Transplantation