

Effect of Diabetes Mellitus on Pharmacokinetics and Pharmacodynamics of Calcineurin Inhibitors Cyclosporine and Tacrolimus

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Purpose. To investigate the pharmacokinetic and -dynamic properties of calcineurin inhibitors (CI) cyclosporine (CsA) and tacrolimus (TAC) in diabetic (D) and non-diabetic (ND) stable kidney transplant patients. **Methods.** Twelve hour, steady-state pharmacokinetic profile of CIs was investigated in 42 patients (22 D, 20 ND) and the concentrations of CsA and TAC were measured by a validated LC-MS/MS method. The pharmacodynamics of CIs was characterized in a subgroup of 18 patients (9 D, 9 ND) by measuring the intra-cellular production of cytokines (Interleukin-2 [IL-2], interferon-gamma [IFN- γ] and tumor necrosis factor-alpha [TNF- α]) in resting peripheral blood lymphocytes (CD3+ cells) using to flow cytometric method reported by Sindhi R. *et al* 2003. Resting cytokine levels in diabetic patients were compared against the ND controls after subtracting background resting cytokine levels from apparently healthy volunteers. **Results.** Exposure to TAC was similar between the two groups (TAC AUC₀₋₁₂ D: 129 \pm 57, ND: 139 \pm 60 ng*hr/mL, p=0.693) whereas exposure to CsA was lower in diabetic patients (CsA AUC₀₋₁₂ D: 1428 \pm 585, ND: 2400 \pm 1235 ng*hr/mL, p=0.048). Significant difference in all three cytokine profiles was observed between D and ND patients. The average IL-2 (Figure A) and IFN- γ (Figure B) levels were significantly lower in the diabetic group (p values of 0.015 and 0.047, respectively). A reverse situation was observed for TNF- α wherein the levels were significantly higher in diabetics (p = 0.012). **Conclusions.** The decreased IL-2 and IFN- γ levels in resting samples indicate increased immunosuppression in diabetics despite similar doses and concentrations of CIs. An increased immune response could explain the fact that diabetics are more susceptible to over-immunosuppression therefore measuring biomarkers of immunity rather than drug concentration may be more beneficial in optimizing drug therapy for these patients.

