

Potential association between mycophenolate, but not tacrolimus, exposure and neutropenia in steroid-free renal transplant recipients

Tony K. L. Kiang¹, BSc, Ph.D., ACPR, Nilufar Partovi¹, Pharm.D., Trana Hussaini¹, Pharm.D., Rebecca Jean Shapiro², M.D., Mary H. H. Ensom³, Pharm.D., FASHP, FCCP, FCSHP, FCAHS

¹Department of Pharmacy, Vancouver General Hospital, Vancouver, BC, Canada, ²Department of Nephrology, Vancouver General Hospital, Vancouver, BC, Canada, ³The University of British Columbia, Children's & Women's Health Centre of British Columbia, Vancouver, BC, Canada

PURPOSE: Over 50% of renal transplant recipients in our center develop neutropenia in the first year while on mycophenolate (MPA) and tacrolimus (TAC) immunotherapy. Although the mechanisms remain unknown, overexposure of MPA and/or TAC may lead to neutropenic episodes. The purpose of this pilot study was to examine associations between MPA/TAC exposure and neutropenia in steroid-free kidney transplant patients.

METHODS: Age, absolute neutrophil count (ANC), white blood cell count (WBC), MPA daily dose (g), TAC daily dose (mg), C1–C2–C4 MPA levels (mg/L), and C0–C2 TAC levels (lg/L) were collected prospectively in adult kidney recipients within 20–40 days post transplant, following written informed consent (N=7). Area-under the curves (AUCs) of MPA and TAC were determined using newly developed and validated limited sampling strategies (LSS) specific to steroid-free regimens (Ther Drug Monit; 33:50–55, 2011). Linear regression and Spearman rank correlation analyses between dose-normalized MPA or TAC and ANC or WBC were conducted (SigmaStat, v3.5 for Windows). Significance was set a priori at $p=0.05$.

RESULTS: Study sample characteristics (mean \pm sd) included: age (52 \pm 16 years), ANC (4.4 \pm 1.8 $\times 10^3$ cells/IL), WBC (6.7 \pm 2.3 $\times 10^3$ cells/IL), MPA dose (1.9 \pm 0.2 g/D), TAC dose (8.3 \pm 3.4 mg/D), LSS-predicted dose-normalized MPA AUC (27 \pm 8 mg*hr/L/g), and LSS-predicted dose-normalized TAC AUC (20 \pm 8 lg*h/L/mg). Statistical analyses revealed a potential inverse association between ANC ($r^2 = 0.30$) or WBC ($r^2 = 0.24$) and MPA exposure, but no such associations were observed for TAC exposure (with $r^2 = 0.02$ for ANC and $r^2 = 0.06$ for WBC, respectively).

CONCLUSION: To our knowledge, this is the first study to examine association between MPA or TAC exposure (calculated using the new steroid-free LSS) and neutropenia in steroid-free kidney transplant recipients. Our novel findings suggest a potential association between MPA, but not TAC, exposure with ANC. More patients are being enrolled to confirm this observation and the utility of the LSS in predicting adverse hematological effects.