Symposium

[S-3] S-3: Biomarkers and TDM of immunosuppressive drugs

Chairs: Uwe Christians, USA / Satohiro Masuda, Japan
2017年9月25日(月) 15:00 ～ 17:00 Main Hall (1F)

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[S-3-4] Determinants of intra-graft tacrolimus concentrations in renal transplant recipients

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キーワード：Tacrolimus, CYP3A5, P-glycoprotein, Kidney, tissue concentrations

Background

Whilst the calcineurin inhibitors (CNI), cyclosporine and tacrolimus, have significantly improved graft survival, their long-term use is limited by nephrotoxicity. Both are substrates for cytochrome P450 3A (CYP3A) and P-glycoprotein (P-gp). P-gp expression determines chronic tubulointerstitial damage in transplanted kidneys and intra-renal cyclosporine concentrations. Although tacrolimus has largely replaced cyclosporine, little is known regarding the factors that determine its intra-renal exposure, and hence potential nephrotoxicity.

Methods

This was a retrospective study in 134 transplant recipients from whom 239 matching blood and renal cortical biopsy samples had been collected between 2-2490 days post-transplantation. Trough blood (C_B) and renal cortex (C_R) tacrolimus concentrations were measured by LC-MS/MS. P-gp expression was assessed by immunohistochemistry in paraffin-embedded biopsy samples. Donor *CYP3A5* genotypes (**1/*1*, **1/*3*, **3/*3*) were determined by TaqMan SNP Genotyping (ThermoFisher Scientific). Univariate and multivariate analyses were used to investigate the relationship between C_B and C_R and: tacrolimus dose, *CYP3A5* genotype, P-gp expression, acute CNI toxicity, generalized proximal tubular injury, rejection and delayed graft function.

Results

C_B ranged from 2.6-52.3 mg/L and C_R from 33-828 pg/mg tissue (n=239). In univariate analyses, there was a weak but significant correlation between C_B and C_R (Spearman r = 0.44, P<0.0001), and C_R/C_B was inversely correlated with time post-transplant (Spearman r = -0.16, P=0.03). In the first month post-transplantation there was no effect of either graft P-gp expression (r = 0.01) or donor *CYP3A5* expressor genotype (P=0.81) on C_R/C_B. However, median C_R/C_B was 1.7-fold higher in patients with acute CNI toxicity compared to those without (P=0.004). Using a linear multiple regression model (R studio), only rejection, time post-transplant, CNI toxicity and rejection:time post-transplant were significant predictors of C_R/C_B (multiple R^2 = 0.06, adjusted R^2 = 0.04, P=0.025).

Conclusions

Blood tacrolimus concentrations only predict 20% of variability in renal tacrolimus concentrations. When adjusted for tacrolimus concentration in blood, graft tacrolimus exposure is not significantly affected by renal cellular clearance pathways (P-gp or CYP3A5). However, it is associated with CNI toxicity and rejection.