Influence of CYP3A5, CYP2C8 and ABCB1 Polymorphisms on Tacrolimus-induced Nephrotoxicity in Liver Transplant Recipients

Yunying Shi [2], Jiangtao Tang [1], Junlong Zhang [1], Yunfei An [1], Yun Liao [1] ,Yi Li [1], Lanlan Wang [1*]

1 Department of Laboratory Medicine, West China Hospital of Sichuan University, Chengdu, Sichuan, China
2 Department of Nephrology, West China Hospital of Sichuan University, Chengdu, Sichuan, China
Correspondence: Lanlan Wang, MD, PhD, Department of Laboratory Medicine, West China Hospital of Sichuan University, Chengdu 610041, Sichuan Province, P. R. China. Email:wangll87@126.com

Objectives

The nephrotoxicity of calcinurin inhibitors (CNI) remains the dominant causative factor for kidney failure in nonkidney organ transplant recipients, especially in liver transplant recipients. The possible influence of single nucleotide polymorphisms (SNPs) including cytocrome P450 3A (CYP3A) subfamily, CYP2C8 and P-gp (ABCB1) on CNI induced renal injury in liver transplant recipients have recently been indicated as one of the most important factors. The purpose of this study was to explore the association between known ABCB1, CYP3A5 and CYP2C8 polymorphisms and the risk of developing tacrolimus (Tac) associated nephrotoxicity in liver transplant recipients.

Methods

A total of 136 living donor liver transplant recipients (107 males and 29 females) and 150 healthy controls (120 males and 30 females) were enrolled in this study. All the recipients had normal renal function (normal Cystatin C and normal urine micro-albumin) before transplantation and received Tac-based immunosuppressive regime (Tac+MMF+ prednisone) afterwards. CYP3A5, CYP2C8 and ABCB1 SNPs were assessed by polymerase chain reaction (PCR) and high-resolution melting curve analysis (HRM analysis). The trough concentrations of Tac were measured by enzyme-multiplied immunoassay technique (EMIT). We also detected serum cystatin C (Cys-C) and urine microproteins including α1 microalbumin (α1M), microalbumin (MA), transferring (TRU) and IgG (IgU) among 136 allo-liver recipients to evaluate whether they have early renal injury and the probable location of the renal lesion.

Results

We could clearly distinguish three genotypes of CYP3A5 and ABCB1, while only two genotypes of CYP2C8 were identified in 136 recipients included. The genotype frequencies of the recipients did not show significant deviation from the Hardy-Weinberg equilibrium (P>0.05). The levels of Cystatin C as well as all the four urine micro-proteins in the recipient group were significantly higher than those in the control group (P<0.05). There was a significant difference in TRU concentration instead of other three microproteins among patients with different CYP3A5 genotypes (P<0.05) (Figure 1). The concentrations of α1M and Cys-C in recipients with CYP2C8*3*1 were significantly higher than that in those with CYP2C8*1*1 allele (p<0.05) (Figure 2 and 3).

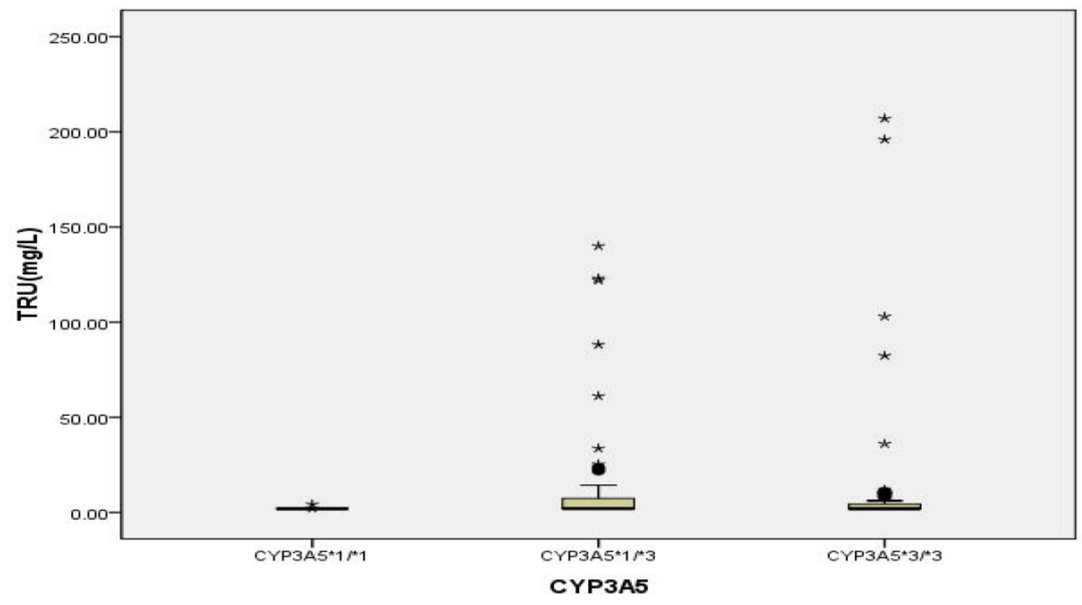

Figure 1 The levels of TRU in diverse CYP3A5 Genotype groups

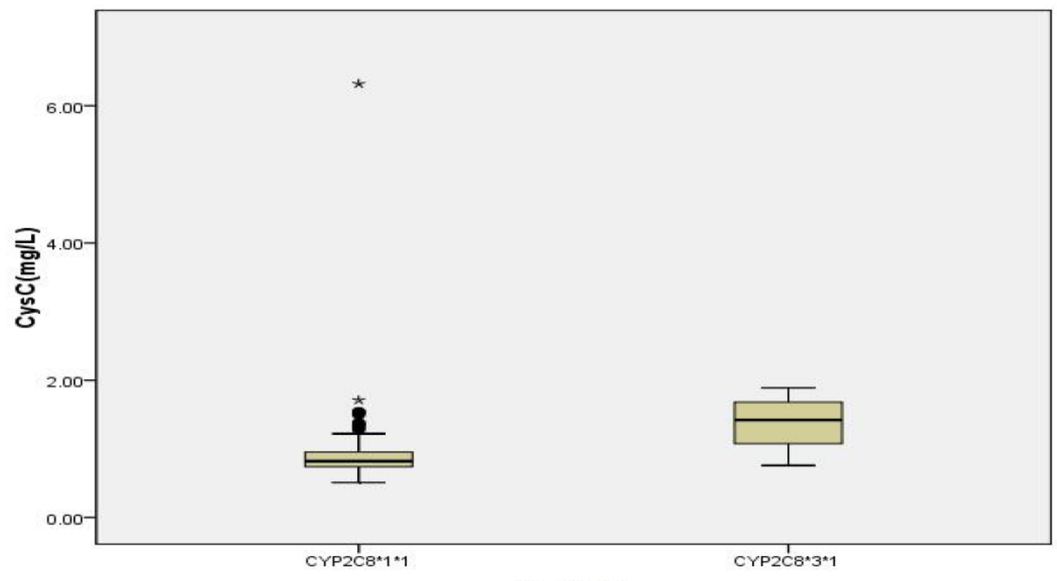

Figure 2 The levels of Cys-C in diverse CYP2C8 Genotype groups

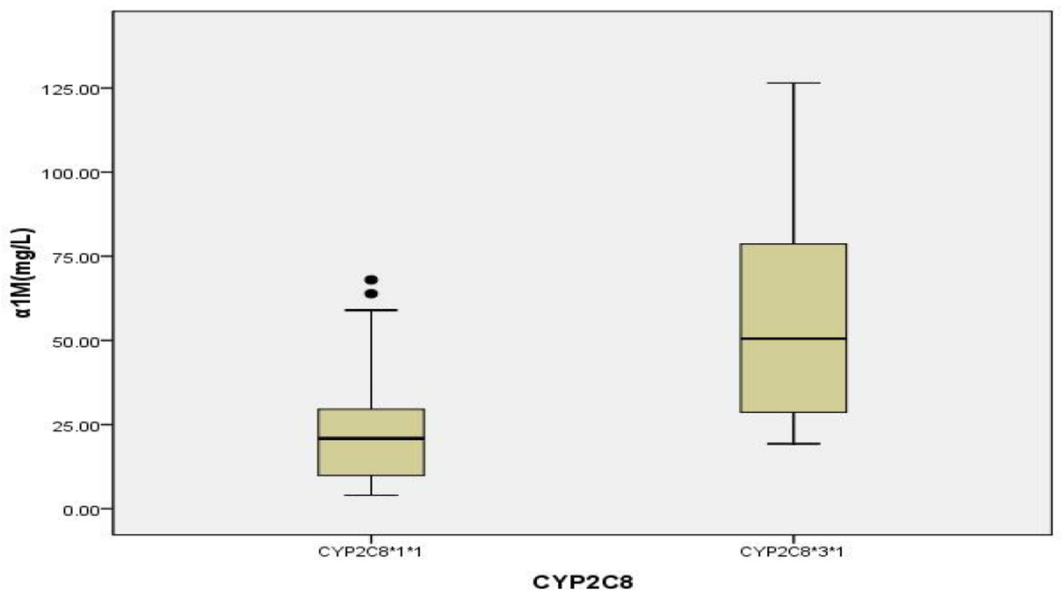

Figure 3 The levels of α1M in diverse CYP2C8 Genotype groups

Regarding MDR1 SNPs C3435T and C1236T, no significant difference was found In Cys-C and urine microproteins among patients with different genotypes.

Conclusions

CYP2C8*3 and CYP3A5*3 might have predictive value on the risk of Tac-induced nephrotoxicity. CYP3A5*3 was associated with the risk of early glomerular injury, while CYP2C8*3*1 was associated with the risk of early tubulointerstitial injury. ABCB1 genotypes (both C3435T and C1236T) were irrelevant to the Tac-induced nephrotoxicity in liver transplant recipients.

West China Hospital of Sichuan University, P.R.C

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