KSN 2017 Abstract

KSN-17-P165

An observational study for Non-invasive detection of tacrolimus toxicity and graft injury using urine cellular RNA expression in kidney transplantation

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Objectives : Although immunosuppressive drugs have improved to reduce renal allograft rejection, renal allograft failure has not markedly diminished. Biochemical examination and invasive biopsy have low sensitivity for diagnosis of tacrolimus toxicity and kidney injury in kidney transplantation. Therefore, the development of non-invasive diagnosis for tacrolimus toxicity and acute and chronic kidney injury using expression level of urinary mRNA is required for long-term graft survival in the kidney transplant patients.

Methods : 110 urine specimens (35 stable, 30 acute rejection (AR), 15 acute calcineurin inhibitor nephrotoxicity (CNI), 10 chronic CNI and 20 acute tubular necrosis (ATN)) were collected after transplantation. RNA extracted from urine pellets was reverse-transcribed and 4 transcripts associated with calcinurin inhibitor toxicity in microarray results published by Maluf et al were investigated using real-time PCR.

Results : Four transcripts (LTF, NNMT, WFDC2, and HIF1A) were selected in published microarray data for diagnosing tacrolimus toxicity by real-time PCR analysis. The expression levels of LTF, NNMT, and HIF1A were significantly decreased in CNI group while 18S were increased. There was no difference of the expression of WFDC2 mRNA between groups. These transcripts discriminated patients with tacrolimus toxicity from patients with ATN and AR. A combination of mRNAs for 18S, LTF, NNMT, and HIF1A that distinguishes CNI from ATN and AR yielded the area under the curve of 0.94 and 0.87, respectively.

Conclusions : We investigated genetic biomarkers to develop a noninvasive

diagnostic assay in urine of kidney transplant patients. These urinary mRNAs may be useful to non-invasively monitor allograft kidney in clinical decisions.

Keywords : kidney transplantation, CNI toxicity, urinary mRNA