Poster

[P25-8] P25-8: Immunosuppressive drugs (3): Biomarkers and pharmacokinetics

Chair: Hideyuki Motohashi, Japan

Mon. Sep 25, 2017 12:30 PM - 1:30 PM Annex Hall (1F)

(Mon. Sep 25, 2017 12:30 PM - 1:30 PM Annex Hall)

[P25-8-8] No influence of CYP3A5*3 and CYP3A4*22 on regain of CYP3A phenotype after kidney transplantation

Kristine Hole[1], Elisabet Storset[2], Ane Olastuen[3], Tore Haslemo[4], Karsten Midtvedt[5], Anders Aasberg[6], Espen Molden[7] (1.Diakonhjemmet Hospital, 2.Oslo University Hospital Rikshospitalet, 3.School of Pharmacy, University of Oslo, 4.Diakonhjemmet Hospital, 5.Oslo University Hospital Rikshospitalet, 6.Oslo University Hospital Rikshospitalet, 7.Diakonhjemmet Hospital)

Keywords: 4beta-hydroxycholesterol, CYP3A4, CYP3A5, phenotype, transplantation

Background

End stage renal disease (ESRD) impairs drug metabolism via cytochrome P450 (CYP) 3A, but it is not clear whether this is reversed after kidney transplantation. Reports regarding change in CYP3A activity after kidney transplantation have been conflicting, describing either increased or decreased metabolic capacity. The aim of this study was to evaluate the change in the CYP3A-biomarker 4β-hydroxycholesterol (4β OHC) concentration after kidney transplantation in relation to *CYP3A4* and *CYP3A5* genotypes, as well as the impact of pre-transplant dialysis on phenotype regain.

Methods

The study included patients who underwent kidney transplantation at Oslo University Hospital Rikshospitalet between January and June 2014. Analyses of *CYP3A4*22* and *CYP3A5*3* variant alleles were performed by real-time polymerase chain reaction and melt curve analyses. Serum concentrations of 4β OHC were determined by an ultra-performance liquid chromatography tandem mass spectrometry method using atmospheric pressure chemical ionization. Linear mixed model analysis with random intercept and random slope was used to evaluate the effects of candidate variables on change in 4β OHC concentration following transplantation.

Results

In total 570 4β OHC measurements from 59 patients were included in the study. Six patients had the reduced-function *CYP3A4*1/*22* genotype, 13 patients had the *CYP3A5*1/*3* genotype, and 41 patients were compound *CYP3A4*1/*1* and *CYP3A5*3/*3* homozygotes. The linear mixed model analysis including all measurements predicted a 0.16 ng/mL increase in 4β OHC per day after transplantation ($p<0.001$), and a 0.5 ng/mL reduction in 4β OHC concentration per kilo increase in bodyweight ($p<0.001$). A linear mixed model analysis solely based on post-transplantation measurements identified not only time since transplantation and bodyweight as significant correlates of 4β OHC concentration, but also creatinine concentration, pre-transplant dialysis status and presence of *CYP3A5*1*. However, these factors did not significantly affect the degree of increase in 4β OHC concentration after transplantation.

Conclusions

This study confirms that CYP3A phenotype is regained after kidney transplantation, but it does not support that the regain in CYP3A activity is dependent on *CYP3A4*/*CYP3A5* genotypes or pre-transplantation dialysis.