Poster

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

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[P25-8-1] Does the CYP3A biomarker 4beta-hydroxycholesterol predict tacrolimus dose early after kidney transplantation?

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Background

Dosing of tacrolimus, a cytochrome P450 3A (CYP3A) substrate, is a major challenge due to unexplained pharmacokinetic variability between patients and over time after transplantation. The objective of this study was to evaluate whether CYP3A phenotyping utilizing the endogenous biomarker 4β-hydroxycholesterol (4β OHC) could help predict the individual dose requirement of tacrolimus early after kidney transplantation.

Methods

Seventy-nine adults contributed a total of 625 4β OHC and 1999 tacrolimus concentrations. The 4β OHC samples were taken immediately prior to and during the first two months after kidney transplantation. The relationship between 4β OHC levels and individual estimates of tacrolimus apparent plasma clearance (CL/F_{plasma}) at different time points after transplantation were investigated using scatterplots and population pharmacokinetic modeling.

Results

There was no significant correlation between pre-transplant 4β OHC levels and tacrolimus CL/F one week, four weeks or eight weeks after transplantation (r=0.20-0.21, p0.06). In the population pharmacokinetic analysis, neither pre-transplant or post-transplant 4β OHC levels explained variability in tacrolimus CL/F (p 0.11). 4bOHC values increased between one week and two months after transplantation (median change +57% [IQR +22-83%], p<0.001), indicating increasing CYP3A activity. Contradictorily, tacrolimus CL/F decreased over the same period (median change −13% [IQR −3-−26%], p<0.001).

Conclusions

Measurements of 4β OHC levels do not improve prediction of individual tacrolimus dose requirement early after kidney transplantation.