Poster

[P25-6] P25-6: Immunosuppressive drugs (1): LC-MS/MS assay

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[P25-6-8] Pharmacokinetics and pharmacodynamics of tacrolimus into its target cells for the longitudinal follow up of liver transplant recipients: looking for new biomarkers for therapeutic drug monitoring

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Background

Tacrolimus (TAC) is a calcineurin inhibitor widely used in liver transplantation. Despite the intensive use of whole blood therapeutic drug monitoring (TDM), some patients exhibit acute cellular rejection or adverse events while having blood levels within the recommended range. The quantification of TAC concentrations in peripheral blood mononuclear cells (PBMC) could be an alternative approach leading to refine TAC TDM as it could better reflect the immunosuppressive (IS) effect and the inhibition of calcineurin (CaN) activity.
This pilot study aimed at assessing the relationships between TAC intracellular concentrations and calcineurin activity in PBMC and describing the relationships between TAC whole blood and TAC intra-PBMC concentrations in 30 liver transplant recipients.

Methods

Intra-PBMC and whole blood TAC concentrations as well as CaN activity were measured at trough at each sampling time (7,14,21,28 days and 6, 8, 12 and 24 weeks post-transplantation) using liquid chromatography-tandem mass spectrometry.

Results

Mean TAC intra-PBMC concentrations were 26.4 ±17.5 pg/10^6 cells and mean CaN activity was 357 ±155 pmol/min/10^6 cells. Throughout the follow-up period, an inverse relationship between TAC Intra-PBMC concentrations and CaN activity was observed, however the correlation was not statistically significant ($p=0.6$). TAC intra-PBMC concentration displayed higher variations with time in the patient group experiencing an acute rejection event than in the group without rejection (ANOVA, $p<0.001$ vs. $p=0.08$). Finally, a poor correlation was found between TAC whole blood and TAC intra-PBMC concentrations ($r^2= 0.25$, $p<0.001$).

Conclusions

According to these preliminary data, the measure of TAC intra-PBMC concentrations is feasible and might be an interesting biomarker of IS drug monitoring. Indeed, it is suggested that PBMC concentrations could be

used as a surrogate longitudinal marker of TAC pharmacodynamics, which is only partially reflected by TAC whole blood concentrations. Further investigations including a larger dataset are needed to confirm these results and to define how intra-PBMC concentrations could be clinically integrated in the next generation of TAC TDM.