P371

P371 -Does chronic kidney disease affect the non-renal elimination of calcineurin inhibitors?

Dr Rajkumar Chinnadurai[1], Mrs Jokha Al-Qassabi[2], Dr Adam Darwich[2], Prof Amin Rostami[2], Prof Philip Kalra[1]
[1]Salford Royal NHS Foundation Trust, Salford, United Kingdom, [2]Centre for Applied Pharmacokinetic Research, University of Manchester, Manchester, United Kingdom

Background and objectives:
The calcineurin inhibitors (CNI), tacrolimus and cyclosporine, are the commonly used immunosuppressants in renal transplant recipients. Both are primarily metabolised by the cytochrome P450 (CYP3A4) enzyme in the liver and eliminated mainly through the faecal route (93%), with only 2.3% through urine. However, it is increasingly evident that the uraemic toxins generated in CKD can alter the hepatic clearance of drugs by a multitude of mechanisms. This study aims to investigate the impact of declining renal function on the non-renal elimination (hepatic clearance) of CNI in renal transplant recipients.

Methods:
60 patients were included in this study from the Salford renal transplant database of 554 patients. They were split into two groups; 30 stable transplant (ST) and 30 failing transplant (FT) patients. The FT group had a rapid decline in renal function (defined as an eGFR drop > 5ml/min/1.73m2 per year). Both the groups included 20 patients receiving tacrolimus and 10 cyclosporine. Data gathered from electronic patient records included demographics, co-morbidities, and concomitant medications at study baseline. Blood results included serial serum liver function tests, haematocrit and eGFR values concomitant with trough drug levels and CNI doses. Pearson's correlation was used to analyse the trend in drug levels with change in eGFR over a median follow-up of 3.5 years. A single compartmental population pharmacokinetic (pop-PK) model was generated and used in the MONOLIX (LIXOFT) software to model the change in hepatic clearance with declining CKD stages.

Results:
At baseline, the median age of our patients was 45 years, predominantly males (65%) and Caucasians (77%). Median body mass index was 23. Patients in the failing transplant (FT) group had a significantly lower haemoglobin and eGFR. Liver function tests (LFTs) were similar between the groups. Median decline in eGFR in the FT group was 6.73 ml/min1.73m2 per year. In the Pearson's correlation analysis eGFR showed a weak positive correlation with both tacrolimus ($r = 0.08$; $p = 0.003$) and cyclosporine levels ($r: 0.20$; $p < 0.001$). The positive correlation persisted for cyclosporine but not for tacrolimus in the partial correlation analysis, after controlling for all confounding variables. The pop-PK models demonstrated an increasing trend of hepatic clearance in both tacrolimus (figure) and cyclosporine with worsening CKD stages.

Conclusion: The positive correlation and increased hepatic clearance observed in our study are suggestive of a possible role of declining renal function on the non-renal clearance of drugs by an alteration in the protein binding of drugs. Further prospective clinical PK studies are warranted for better quantification of these changes and to guide accurate dosing.