Poster

[P26-6] P26-6: Immunosuppressive drugs (5): Clinical practice

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[P26-6-7] Therapeutic drug monitoring of everolimus depends on concomitant immunosuppressant in heart transplant patients —preliminary pharmacokinetic observation

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Background

The aim of the study was to compare everolimus (EVE) pharmacokinetics in heart transplant patients treated with EVE in co-therapy either with cyclosporine (CSA), tacrolimus (TAC) or mycophenolate mofetil (MMF).

Methods

A number of 15 steady-state pharmacokinetic profiles were obtained from 15 patients (12M, 3F; mean age 52 y. (24-68)) after heart transplantation treated with EVE + CSA (n=6), EVE + TAC (n=5) or EVE + MMF (n=4). Immunosuppressants dosages were guided by TDM (LC-MS/MS for TAC, CSA, EVE in blood, a specific HPLC-UV for MPA in plasma). Non-parametric approach was used for pharmacokinetic evaluation.

Results

Mean EVE dose was: 1.00 ±0.32, 1.85 ±0.60 and 2.00 ±0.68 mg/d in CSA, TAC and MMF groups, respectively ($p<0.05$ for CSA-TAC and CSA-MMF, NS for TAC-MMF; Mann-Whitney U test). These EVE doses resulted in C_{min} of: 5.80 ±0.94, 5.40 ±2.57 and 4.20 ±0.83 ng/mL, and in AUC_{0-12} of: 92.90 ±10.17, 86.10 ± 31.08 and 70.48 ±11.18 ng·h/mL, respectively for EVE + CSA, EVE + TAC and EVE + MMF ($p<0.05$ for CSA vs. MMF for both C_{min} and AUC_{0-12}).

However, if pharmacokinetic parameters were corrected for daily dose, both C_{min}/D and AUC_{0-12}/D were found significantly higher in patients co-receiving CSA, yielding for C_{min}/D: 6.08 ±1.38 $L^{-1}\cdot10^{-3}$ vs. 2.84 ±0.82 (TAC, $p<0.01$) or vs. 2.18 ±0.43 (MMF, $p<0.01$) as well as for AUC_{0-12}/D: 98.66 ±24.39 $h\cdot L^{-1}\cdot10^{-3}$ vs. 46.62 ± 9.47 (TAC, $p<0.01$) or vs. 36.67 ±6.21 (MMF, $p<0.01$).

Because our group of patients was (currently) relatively small, therefore the analysis of 154 trough samples from routine EVE monitoring was included to support the pharmacokinetic observation. Similar findings to the results presented above for pharmacokinetic parameters, were noted for dose corrected EVE C_{min}/D values: 5.84 ±2.40 $L^{-1}\cdot10^{-3}$ (CSA, n=28) vs. 2.49 ±0.73 (TAC, n=50, $p<0.0001$) or vs. 3.11 ±2.13 (MMF, n=76, $p<0.0001$).

Conclusions

Our observations supported the hypothesis on lack of pharmacokinetic interaction between EVE and MMF (similarly to EVE-TAC but contrary to EVE-CSA). Co-administered immunosuppressive drug needs to be considered for setting optimal EVE maintenance dose.