INFLUENCE OF CYP3A4*1 AND CYP3A4*22 GENETIC POLYMORPHISMS ON MELTDOSE® TACROLIMUS PHARMACOKINETICS IN ADULT RENAL TRANSPLANT PATIENTS

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BACKGROUND

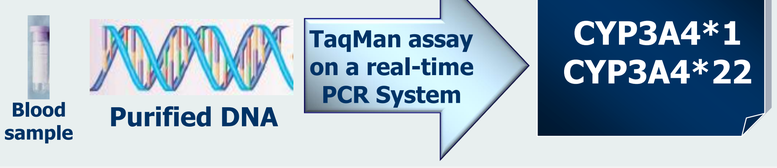
Tacrolimus shows a narrow therapeutic range and wide interindividual variability in its pharmacokinetics. The CYP3A4*1 and CYP3A4*22 polymorphisms could influence on its dose requirements.

Aim: To evaluate the impact of CYP3A4*1 and CYP3A4*22 genetic polymorphisms on dose requirements, trough concentrations and trough concentrations/dose ratio of the once-daily prolonged-release tacrolimus formulation with a MeltDose® technology (LCP-Tacro) at different post-transplant moments in adult renal transplant patients.

PATIENTS AND METHODS

- ❑ RETROSPECTIVE STUDY.
- ❑ POPULATION OF ESTUDY:
  - ➢ 45 Caucasian renal transplant patients treated with an LCP-Tacro-based immunosuppressive regimen.

GENETIC DETERMINATION



MEASUREMENT OF TACROLIMUS BLOOD LEVELS

Pharmacogenetic variables

- ➢ CYP3A4*1: TT (wild type) vs. TC+CC (variant carriers)
- ➢ CYP3A4*22: GG (wild type) vs. GA+AA (variant carriers)

15 days (15D); 1 (M1), 3 (M3), 6 (M6), 12 (M12) and 24 months (M24) after transplantation

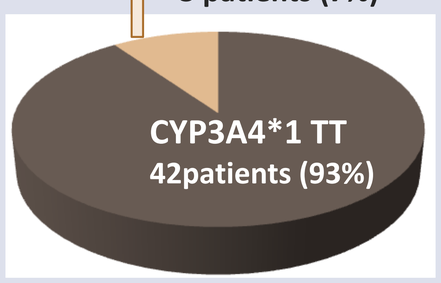
Pharmacokinetic variables

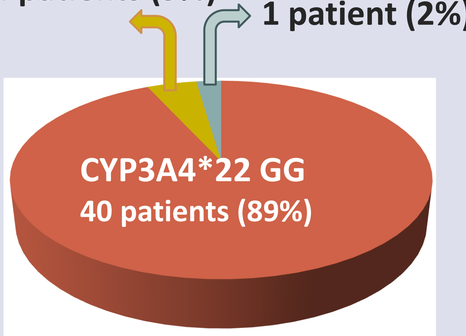
- ➢ Dose requirements: Daily dose –D- and weight-adjusted daily dose -D/kg-
- ➢ Trough concentration –C_{trough}-
- ➢ C_{trough}/D ratio

STATISTICAL ANALYSIS: SPSS version 19.0. Mann-Whitney test was used. $p<0.05$: statistically significant.

RESULTS

45 patients (p), 59 years, 74 kg





CYP3A4*22 GG vs. GA + AA

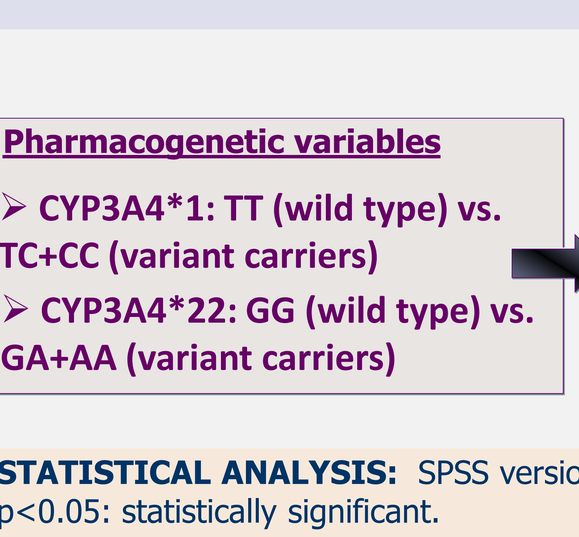
GG vs. GA+AA

$p<0.05$

Daily dose (D) (mg/day)

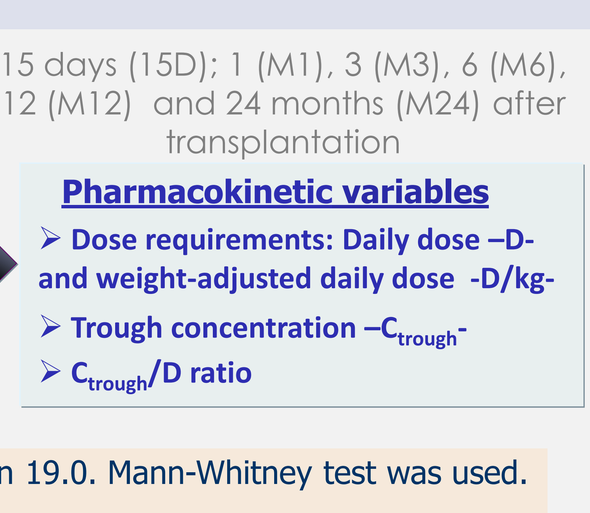
M1

Weight-adjusted daily dose (D/kg) (mg/kg/day)



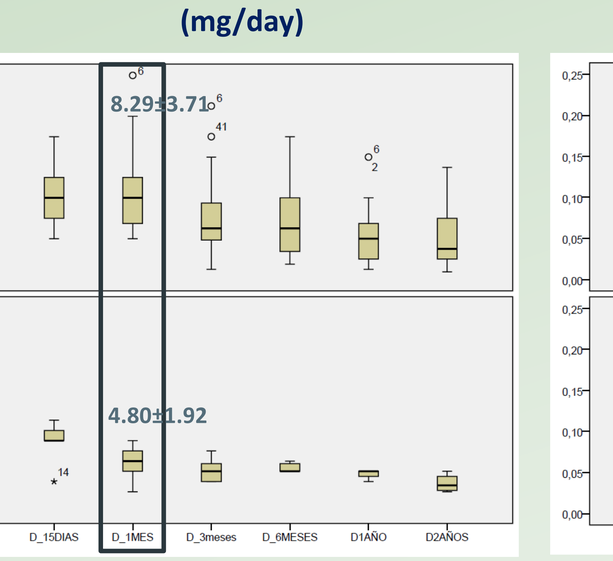
M1

Concentration /Dose ratio (C_{trough}/D) (ng/mL per mg/kg/day)



M1

C_{trough} (ng/mL)



M24

CYP3A4*1: The CT carriers showed a non-statistical trend towards higher daily dose with respect to TT carriers.

Non significant changes for other pharmacokinetic parameters and other post-transplant moments

CONCLUSION

CYP3A4*22 seems to influence on dose requirements and trough concentrations in patients treated with LCP-Tacro. However, we found no evidence of significant association of CYP3A4*1 with the pharmacokinetic parameters evaluated. In clinical practice, CYP3A4*22 could be of value in personalizing the tacrolimus dose requirements.

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