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-released tacrolimus formulation with a MeltDose® technology (LCP-Tacro) at different post-transplant moments in adult renal transplant patients.

Patients and methods: 45 Caucasian renal transplant patients treated with an LCP-Tacro-based immunosuppressive regimen were included. Whole blood trough concentrations were measured by a chemiluminescent immunoassay on the ARCHITECT™ platform. A TaqMan assay on a real-time PCR system was used for the genotyping of CYP3A4*1 and CYP3A4*22 polymorphisms which were correlated to dose requirements: daily dose and weight-adjusted daily dose, trough concentrations and dose-adjusted trough concentrations at 15 days, 1, 3, 6, 12 and 24 months after transplantation. Statistical analysis was carried out using SPSS. Mann-Whitney test was used. $P<0.05$ was considered statistically significant.

Results: The study included 45 patients, age 59 years and weight 74 kg. The genetic variants identified for CYP3A4*1 were: TT in 42 patients (93%) and CT in 3 (7%) and for CYP3A4*22: GG in 41 patients (989%), GA in 2 (9%) and AA in 1 (2%).

When patients were grouped according to CYP3A4*22 genotype, at 1month, there was a significant increase in dose requirements in GG carriers in comparison with the GT carriers (daily dose: 8.29±3.71 vs. 4.80±1.92 mg/day; weight-adjusted daily dose: 0.11±0.04 vs. 0.07±0.03 mg/kg/day) to obtain significant lower concentration-dose ratio: 95.36±36.10 vs. 144.60±34.83 ng/mL per mg/kg/day. At 24 months, levels were significantly lower in GG carriers in comparison with the CT carriers (7.14±1.74 vs. 10.75±3.17 ng/mL), but not the dose requirements.

For the CYP3A4*1 genetic polymorphisms, the CT carriers showed a non-statistical trend towards higher daily dose with respect to TT carriers.

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.

Key words: LCP-Tacro, CYP3A4*1, CYP3A4*22, pharmacokinetics