DISTRIBUTION OF CYP3A5 AND MDR-1 SINGLE NUCLEOTIDE POLYMORPHISMS IN CAUCASIAN LIVER TRANSPLANT PATIENTS

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Background and objective: Tacrolimus (TAC) is an immunosuppressive drug widely used in liver transplant patients. Due to its narrow therapeutic index and high inter-intra-individual pharmacokinetic variability, it is necessary to closely monitor its administration regimens. TAC, like other drugs commonly used in transplantation, is a substrate of cytochrome P-450 (CYP) 3A4 and 3A5 enzymes, as well as of the product of the MDR-1 gene, the drug transporter P-glycoprotein (P-gp). It has been suggested that differences in the expression levels and in the bioactivity of CYP3A5 and P-gp due to single nucleotide polymorphisms (SNPs) can influence TAC dose requirements. We are investigating the effects of possible relevant CYP3A5 and MDR-1 SNPs (analyzed both in liver donors and recipients) on TAC blood concentrations achieved in liver transplant patients.
Methods: To date we have studied 13 Caucasian liver transplant patients treated with TAC alone or combined with steroids and/or mycophenolate mofetil. Possible co-administered drugs known to interact with CYP3A and P-gp were recorded. At one month after transplantation, TAC doses (D) and trough blood concentrations (C) were detected and C/D ratios were obtained by dividing the TAC trough levels (ng/ml) by the corresponding 24 h doses (mg/kg). Genomic DNA of each liver donor and corresponding recipient was extracted from 2-3 ml EDTA anticoagulated blood using a QIAamp DNA Mini Kit (Qiagen, Italy). Polymerase chain reaction (PCR) followed by restriction fragment length polymorphism analysis was used for genotyping CYP3A5*3 and MDR-1 at exon 26 [C3435T] and exon 21 [G2677T].
Results: Data on C/D ratios (mean ± SD = 122.8 ± 76.6) confirmed the wide inter-individual variability with respect to TAC pharmacokinetics. For CYP3A5 SNP, all recipients were homozygous for the CYP3A5*3 variant allele, which yields a non-functional enzyme. Among the donors, 12 (92.3%) were homozygous for the *3 allele and 1 (7.7%) was heterozygous for the variant allele (*1/*3). For the MDR-1 G2677T polymorphism, GG, GT and TT genotypes were detected in 11 (84.6%), 0 and 3 (15.4%) of recipients, respectively. Of the donors, 9 (69.3%) were homozygous for the wild-type allele; 3 (23%) were heterozygous and 1 (7.7%) was homozygous for the variant allele. For the MDR-1 C3435T polymorphism, CC, CT and TT were detected in 2 (15.3%), 7 (53.8%) and 4 (30.9%) of the 13 recipients. The same genotypes were distributed in 30.9%, 46.1% and 23% of the donors, respectively.
Conclusions: The preliminary data collected so far show high C/D ratios in Caucasian liver transplant recipients. They suggest also that, since in our population there is a very strong predominance of the CYP3A5 non-expressor genotype, CYP3A5*3 analyses might rarely pre-identify patients who need TAC dose modifications.