

The usefulness of pharmacogenetic information in liver transplantation

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Scope of the lecture:

The scope of this lecture reflects the influence of donor and recipient *CYP3A5*3*, *CYP3A4*22* and *ABCB1* genotypes on Tacrolimus pharmacokinetics and renal dysfunction in adult and pediatric liver transplant recipients, as well as the need to carry out multicenter prospective randomized clinical trials to properly qualify the clinical utility of genotyping these single nucleotide polymorphisms before liver transplantation.

Learning objectives:

1. *CYP3A5*3* and *CYP3A4*22* alleles may explain in part the inter-individual pharmacokinetic variability and differences in initial tacrolimus dose-requirement, and clinical outcome in liver transplant recipients.
2. Donors carrying the *CYP3A4*22* T allele show a significant decrease in tacrolimus apparent clearance and 2-fold average increase in C_0/D ratio.
3. *CYP3A4* genotype of donors combined with *CYP3A5* of donor and recipient genotypes significantly influences tacrolimus blood concentrations in recipients and reflects the risk of tacrolimus over or underexposure.

Extended abstract:

Previous studies in liver transplant aim to characterize the clinical impact of donor and recipient genotypes on calcineurin inhibitors pharmacokinetics.

Focus on tacrolimus (Tac) interindividual pharmacokinetic variability, some studies in liver transplant evaluated the influence of the *CYP3A5*3*, *CYP3A4*22* and *ABCB1* genetic polymorphisms in donors and recipients on Tac dose requirement and clinical outcomes, with special emphasis in the incidence of acute rejection and nephrotoxicity.

The obtained results demonstrate that both donor and recipient *CYP3A5* genotype significantly influence Tac pharmacokinetics in adult and pediatric populations. The required daily dose of Tac was approximately 2-3 times higher in carriers (recipients or/and donors) of at least 1 *CYP3A5*1* allele (expressing a functional *CYP3A5* enzyme). In a meta-analysis (n=336 patients), the rate of acute rejection was about 3-fold higher at first month in recipients expressing this metabolizing enzyme than in non expressors (*CYP3A5*3/*3*).

The influence of *CYP3A4*22* genotype on dose-normalized trough concentration (C_0/D) was observed in donors carrying the *CYP3A4*22* T allele, with a significant decrease in Tac apparent clearance about 30% and 2-fold average increase in C_0/D ratio. No significant effect of the recipient's intestinal *CYP3A4*22* T allele on Tac pharmacokinetics was observed, only few studies reported a significant effect of *CYP3A4*22* genotype on recipients at first week after transplantation, however as time passed the *CYP3A4*22* genotype of the engrafted livers had a stronger influence on Tac pharmacokinetics than the recipients' genotype. This is in agreement with the notion that early post-transplantation the intestinal metabolism by the

recipient is critical and its genotype influences Tac pharmacokinetics, but later in time the hepatic metabolism by the engrafted liver becomes more important.

Concerning Tac renal dysfunction none of the *CYP3A5*3*, *CYP3A4*22* and *ABCB1* genetic polymorphisms evaluated in donors and recipients had a significant impact on renal function long-time after transplantation, but some studies showed an association between *CYP3A5* genotype and Tac-related nephrotoxicity.

In summary, genotyping these single nucleotide polymorphisms before liver transplantation in donors and recipients might be helpful for selecting the adequate initial daily Tac dose and to achieve target concentrations. Nevertheless, prospective data from multicenter randomized clinical trials are required to better qualify the clinical utility of genotyping these polymorphisms.

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