

Genotype-Guided Immunosuppression after Liver Transplantation: Chance for Individualizing Therapy?

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Organ transplantation has become an important additional option for patients with organ failure. The immunosuppressive drugs used worldwide after transplantation has a narrow therapeutic index and high inter-individual variations. Overdosing may lead to toxic side-effects, such as infection, malignant diseases or renal dysfunction. Drug levels below the therapeutic range result in sub-optimal immunosuppression and increased risk of acute rejection [1,2]. Especially early after transplantation an efficient and safe achieving of target blood concentrations is important. Intensive drug monitoring is necessary to keep drug levels within therapeutic range. An important goal in transplantation is to tailor immunosuppression to the individual needs of the patient, avoiding both rejection and over-immunosuppression. Opportunistic infections and malignancies remain a significant cause of death after transplantation and are obvious consequences of over-immunosuppression.

In the past years therapeutic drug monitoring has helped physicians to make dosage recommendations based on the individual patient's drug exposure. Currently, monitoring of immunosuppression is conducted mainly on the basis of pharmacokinetic characteristics, which do not necessarily predict clinical outcome in the individual. The question is whether genotyping of the recipient may lead to further individualization of immunosuppressive therapy in transplant patients and whether genotyping might be helpful in determining an appropriate starting dose.

Early studies have shown that pharmacogenetics may provide additional information on how individual genes may affect the response to medications.

Some clinical studies have shown that carriers of the *CYP 3A5* *1 allele require a higher dose of Tacrolimus to achieve the desired drug levels than homozygous carriers of the *CYP 3A5* *3 allele [3-6]. The correlation of the *CYP 3A5* genotypes with the dose of Tacrolimus in renal transplant patients was evaluated in a few case series with small sample size and / or short observation time [7-9]. In a few studies the effect of the *CYP 3A5* genotypes on the clinical outcome was evaluated. The risk of early acute organ rejection [10], the incidence of delayed graft function [11] and the emergence of calcineurin inhibitor-associated nephrotoxicity [12] were identified. Most pharmacogenomic studies after transplantation investigated renal transplant recipients. Results from patients after liver transplantation are currently very rare and not sufficient to draw conclusions about the clinical relevance.

In a recent European consensus conference the convincing association between *CYP 3A5* genotypes and Tacrolimus level concentrations was confirmed [13]. The clinical benefit is currently still unclear and further research in this area has been requested to make clear recommendations possible.

The aim of personalized medicine or individualized treatment is to match the right drug to the right patient. The appropriate treatment for a patient according to his/her genotype could be designed.

Pharmacogenomics could offer the possibility to individualize immunosuppressive therapy based on the patient's genetic profile. However, the clinical applicability of this approach is still to proven. Pharmacogenomics represent still an exciting challenge for the future. Journal of liver could be a discussion forum for this topic and thereby make a contribution to progress in this area.

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