

Clinical Implementation for Pharmacogenetics of Immunosuppressive Drugs: European Multicentric Report. Barcelona 2009.

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Introduction

In the field of transplantation, personalized immunosuppressive drug therapy is essential for preventing allograft rejection. This treatment has to be efficient and safe enough to permit a good quality of life for transplant recipients. Individualizing immunosuppressive patients' treatment to achieve the optimal balance between therapeutic efficacy and occurrence drug-toxicity is the physician's objective.

It is well known that gene polymorphisms may be predictive of pharmacokinetic and pharmacodynamic outcomes after transplantation. Previous studies have shown that some polymorphisms in gene encoding for proteins involved in immunosuppressive-drug transport and metabolism may play a role in the exposure and effect of these agents.

Genetic polymorphisms in *CYP3A5*, *CYP3A4*, *MDR1*, *UGT1A9*, *MRP2* and *TPMT* have an impact on tacrolimus, MPA and Azathioprine metabolism and transport. The exact contribution for patient care is being evaluated in multi-centric clinical trials and single centre experiences with the aim to study their impact on drug exposure and the incidence of rejection and adverse events.

It is of importance to consider that practically all these studies have been carried out in renal transplant recipients (Caucasian, Black, Japanese and Chinese populations). As a consequence, no conclusive data with reference to the clinical impact on liver (only few data from Asian populations), heart and lung recipients are known.

More recently, the introduction of some of these polymorphisms' analysis in routine has been considered, particularly for specific populations in which these analyses may help to better understand the clinical outcome of these patients. Often patients treated with tacrolimus and / or MMF may suffer from adverse events related to the administered drug/s even though these drugs are within the therapeutic range. In addition, another clear example could be those patients that need significantly higher doses – in comparison with recommended schemes - to reach target concentrations.

Currently, with the aim of introducing the analysis of these polymorphisms for immunosuppressive drugs in the field of solid organ transplantation in a rational way, a round table meeting about the clinical implementation for pharmacogenetics of immunosuppressive drugs, involving seven centers with wide experience in transplantation in Europe was organized in Barcelona last March 3.

The Goals of This Round Table Were:

- 1) To evaluate previous single centre experiences in the analysis and report of some of these polymorphisms in routine.
- 2) To analyze the role of pharmacogenetics for specific populations.
- 3) To agree upon the most appropriate request for the analysis and the specific parts of the report of results.

Results and Agreements Reached at the Round Table :

- 1) To evaluate previous single center experiences in the analysis and reporting some of these polymorphisms in routine.**

All the centers involved have wide experience in the analysis of these polymorphisms in research, but not in routine. Only one center, from Rotterdam, has previous experience in the analysis of CYP3A5 and TPMT for tacrolimus and azathioprine metabolism in the field of immunosuppression in routine, whereas the center from Goettigen performs only the analysis for TPMT in routine (the only genetic polymorphism analysis for immunosuppressive drugs accepted by the FDA). Of great importance is the emergence in all centers of a growing interest from physicians and pharmacologists, to introduce in routine the analysis of those polymorphisms, which could be of interest in clinical practice for a more efficient handling and administration of some immunosuppressive drugs.

On this point, all the participants considered some important aspects of the whole procedure:

- There is a need for patient information and consent (except in the Netherlands).
- Also there is a need for the consent from the donor, and in the case of cadaveric donors, in some countries in Europe, the consent must come from the donor's family.
- In every sample, only polymorphisms in relevant genes for immunosuppression will be investigated. We have to consider that in many countries only the specific genes requested by the physician could be analyzed. For other polymorphism analysis a new consent must be required.
- Specific request form for pharmacogenetic analysis, of some immunosuppressive drugs, that includes the reason (prior screening or experienced side effects, relevant co-medication) for the SNPs analysis must be filled in.
- Report of the results should contain specific parts on genotyping (SNPs, methodology, allele frequencies, effects), its interpretation (with background from the literature) and specific advice.

2) To analyze the role of pharmacogenetics for specific populations.

At present, since there is no data supporting systematic analysis of these polymorphisms in all patients to be treated, the request for some specific SNPs should be based on clinical reasons in treated patients.

Pharmacogenetic analysis should be carried out only in relation to specific immunosuppressive drug therapy (not potential drugs).

- CYP3A5 for tacrolimus, particularly in those centers with no frequent incidence of TAC pharmacokinetic monitoring (less than 2 analyses per week, particularly early post-transplant period).
- TPMT for azathioprine therapy
- The analysis of MDR1 in donor (blood and kidney biopsy) and recipient seems to be of interest as a predictor of the risk of developing nephrotoxicity, but further studies in transplant recipients are needed to reach conclusions on this topic.
- With reference to MPA, UGT1A9 polymorphisms seem to play a notable role in its exposure and effect. Currently, few studies in kidney transplant recipients have been carried out and we need more time to draw conclusions.

Further studies in solid organ transplant recipients are needed for evaluating the application of these SNPs in routine.

3.1) Parts of the Request of Pharmacogenetic Analysis

- Patient ID:
- Immunosuppressive Therapy involved in the treatment (Drug, Dose, Blood concentration).
- Clinical reason for request (Screening prior to therapy, High blood Concentrations, Low blood concentrations, No effects, Side effects).
- Co-medication
- Contact information from requesting physician
- Authorisation: Who is responsible for requiring the SNPs Analysis?

3.2) Parts of the Report of Pharmacogenetic Analysis

Patient ID

Request Test:

Problem/request: screening for a specific genetic polymorphism.

Material: EDTA blood or other biological matrix.

Analysis for: specific SNPs.

Results:

Conclusion: allele carrier observed for each SNP

Interpretation Advice: predictive of

Background interpretation: based on results from previous studies, the analyzed SNPs may be associated with efficacy of the drug or the risk to develop adverse events (The interpretation of the results predicts normal, slow or fast metabolism).

Background of the test:

Allele frequency: for Caucasians; Africans; Asians....

General considerations: some general sentences could be of interest for the physicians (related to: Pharmacokinetic interactions co-medication. Liver and Renal function, HIV, HCV, EBV, CMV)

Authorization: Who is responsible for signing the report?

This first agreement on Pharmacogenetics on Immunosuppression should be updated in a near future considering the new results from multicentric clinical trials in liver, kidney and heart transplantation.