Pharmacogenetics as a tool to tailor the immunosuppressive therapy: focus on azathioprine and tacrolimus

Pharmacogenetics as a tool to tailor the immunosuppressive therapy: focus on azathioprine and tacrolimus

Loredana Serpe[1], Pier Luigi Calvo[2], Andrea Brunati[3], Antonio Amoroso[4], Renato Romagnoli[3], Roberto Canaparo[1]

[1]Departimento di Scienza e Tecnologia del Farmaco, Università degli Studi di Torino (loredana.serpe@unito.it)
[2]Department of Paeditric and Public Health Sciences, University of Torino, Italy
[3]Department of Surgical Sciences, University of Torino, Italy
[4]Department of Medical Sciences, University of Torino, Italy

Pharmacogenetics research looks at variations in the human genome and ways in which genetic factors might influence individual's response to drugs. We performed two pharmacogenetic studies on the immunosuppressive drugs, azathioprine and tacrolimus, to investigate the role of drug-metabolizing enzyme polymorphisms, alone or in combination with physiological factors, in avoiding severe drug reaction or in reducing pharmacokinetic (PK) variability.

Azathioprine is a thiopurine drug, used mainly in acute lymphoblastic leukaemia, organ transplant and autoimmune disorders. The thiopurine methyltransferase (TPMT) enzyme is one of the major metabolizing enzymes of azathioprine and its activity level in human tissues is controlled by a common genetic polymorphism. Therefore, an azathioprine dose reduction is recommended to avoid severe adverse drug reactions in patients carrying mutations with a decreased TPMT activity. We investigated the TPMT genotype-phenotype relationship in a healthy unrelated population and a concordance rate of 71.6% between genotype and phenotype was observed. Interestingly, genetic factors seemed to be the major determinant of TPMT phenotype variability in adults, whereas wild type children showed a significantly higher TPMT activity compared to wild type adults, showing also significant differences according to the gender. Therefore, not only the genetic factors but also physiological features, such as age and gender, should be taken into consideration when assessing the TPMT phenotype.

Tacrolimus is an immunosuppressive drug widely used in patients undergoing solid organ transplantation. This drug has a narrow therapeutic index, exposing patients to acute graft rejection and toxicity in cases of low or high blood concentrations, respectively. Therefore, it has been suggested to analyze some genetic factors, such as polymorphisms in genes coding for biotransformation enzymes like cytochrome P450 isoenzyme 3A5 (CYP3A5), in order to reduce the great inter-individual PK variability after the initial tacrolimus dose.

We investigated the influence of the CYP3A5 donor genotype in pediatric patients after liver transplantation correlating this with tacrolimus disposition on the first day of treatment. We confirmed that tacrolimus starting dose in pediatric liver transplant patients may be influenced by the liver donor's CYP3A5 genotype but, again, also sex and age appeared to be associated with tacrolimus disposition.

In conclusion, these studies emphasizes the fact that tailoring the azathioprine or tacrolimus dosage according to genetic and physiological factors in pediatric patients could improve the efficacy of these immunosuppressive therapies.