Tacrolimus Therapeutic Drug Monitoring in Stable Kidney Transplantations and Individuations of CYP3A5 Genotype

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In organ transplantations, Tacrolimus (TAC) dosing is routinely directed by Therapeutic Drug Monitoring (TDM). However, sometimes patients reach the concentrations target (CT) quickly, but sometimes arrive to reach this CT slower and could potentially increase the risk of graft-rejection due to under-exposure to TAC. Since CYP3A5 may play a dominant role in the metabolism of tacrolimus [1], we studied the CYP3A5 genotype, as part of a routine TDM of the TAC, in patients with very high doses of TAC, to confirm them as extensive metabolizer (EM). We focused on CYP3A5 6986A > G, the most important polymorphism related to TAC metabolism in which the wild-type genotype is CYP3A5*1 and its variant is CYP3A5*3 [2].

In 2016 the SOC Institute of Clinical Pharmacology has performed TDM TAC of transplanted kidney stable for over a year. The immunosuppressive therapy was TAC, Mycophenolate Mofetil and prednisone. The patients were not taking drugs inducing or inhibiting the TAC. All patients had stable liver and kidney functions. One year after transplantation, the blood concentration TAC target (CT) was 5-8 ng/ml. We use an immunoassay methods for TAC (ACMIA on a Siemens Dimension® Integrated Chemistry Systems Tacrolimus) . The patients were divided in two groups on the TAC doses at the moment of TDM: Group 1, patients with TAC daily doses <6 mg/24 hours; Group 2, patients with TAC daily doses> 6 mg / 24 hours. The doses were transformed in 1 mg/Kg. All patients have been undergone to Sanger sequencing of CYP3A5 gene to characterize CYP3A5 polymorphisms. Patients with CYP3A5*1 and *1/*3 are considered extensive metabolizer (EM), while ones with CYP3A5*3 are poor metabolizer (PM) [3]. For statistics we have used Sigma Stat and results were considered significant when p <0.05.

We ran the TDM of the TAC in 22 stable renal transplant for more than a year. Their mean age was 51±14 years , and the mean weight was 64.9 ±14.3 Kg. All patients had reached CT and the mean daily dose of TAC > one year was 11.8 ±11.2 mg . However the group 1 and 2, presented the TAC mean dose (dose/Kg) at the moment of TDM of 2.9± 1.4 (0.05±0.03 mg/Kg) and of 12.5 ± 3.5 (0.2±0.05), respectively. The difference of the mean dose at the time of the TDM, was statistically different (p <0,001). Analysing the CYP3A5 genotype, we demonstrated that Group 1 presents the PM genotype, while Group 2 could arbour both PM and EM polymorphisms.

The TAC is one of the most commonly used immunosuppressants for solid organ transplantation. The clinical use of TAC is complicated by its high pharmacokinetic variability among patients as well as its narrow therapeutic index. This can lead to underexposure, which potentially increase the risk of rejection, or overexposure to the risk of toxicity such as nephrotoxicity, hypertension, hyperglycemia, and neurotoxicity.

The variability in blood concentrations of TAC is partially dependent on variations in the CYP3A5 gene. In kidney transplants, individuals with genotype CYP3A5 *1/*1 or *1/*3 have minor

adjustments of significantly lower doses compared with the genotype CYP3A5 *3/*3, with the expression 1, which requires doses 1.5 to 2 times the required dose to reach the target concentrations [4].

CYP3A5 genotype guided dosing can achieve initial target TAC concentrations more quickly after transplantation. Faster achievement of target concentrations could potentially reduce the risk of graft-rejection due to under-exposure.

This study shows that the cooperation between the Nephrology, Clinical Pharmacology and Genetics may optimize therapy with TAC to achieve faster CT in order to reduce the risk of rejection and welfare cost.

Bibliografy

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