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THE ROLE OF CYP3A5 GENOTYPE AND TACROLIMUS MONITORING IN STABLE KIDNEY TRANSPLANTATIONS

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INTRODUCTION AND AIMS: Despite Tacrolimus (TAC) dosing is routinely directed by Therapeutic Drug Monitoring (TDM), some patients reach the

concentrations target (CT) quickly, while others achieve the same CT slower, increasing the risk of graft-rejection caused by TAC under-exposure.

METHODS: We studied the CYP3A5 genotype in patients receiving very high doses of TAC, to confirm them as extensive metabolizers (EM) [1]. 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]. We performed TAC TDM among kidney transplant (KTx) recipients who were clinically stable for over a year. The immunosuppressive regimens included TAC, mycophenolate mofetil and corticosteroids for all patients. All patients had stable liver and kidney functions and concomitant TAC inducing or inhibiting drugs. One year after transplantation, the target blood concentration of TAC (CT) was 5-8 ng/ml. We use an immunoassay method to measure TAC levels (ACMIA on a Siemens Dimension® Integrated Chemistry Systems Tacrolimus). The patients were divided in two groups based 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 uniformed to 1 mg/Kg. All patients underwent Sanger sequencing of CYP3A5 gene to characterize CYP3A5 polymorphisms. Patients with CYP3A5*1 and *1/*3 were considered extensive metabolizer (EM), while the ones with CYP3A5*3 were poor metabolizer (PM) [3]. Statistical analysis was performed using Sigma Stat and results were considered significant when $p < 0.05$.

RESULTS: A total of 22 KTx recipients were included in the study. Mean age was 51±14 years. Mean weight was 64.9 ±14.3 Kg. All patients had reached CT with mean daily dose of TAC after at least one year from transplantation of 11.8 ±11.2 mg. Group 1 and 2 mean doses (dose/Kg) at the moment of TDM were 2.9± 1.4 (0.05±0.03 mg/Kg) and 12.5 ± 3.5 (0.2±0.05), respectively ($p < 0{,}001$). Analysing the CYP3A5 genotype, we demonstrated that Group 1 presents the PM genotype, while Group 2 could arbour both PM and EM polymorphisms. The clinical use of TAC is complicated by its high pharmacokinetic variability among patients as well as its narrow therapeutic index. This can lead to under-exposure, which potentially increases the risk of rejection, or over-exposure with the risk of toxicity such as nephrotoxicity, hypertension, hyperglycaemia, and neurotoxicity. TAC blood concentrations variabilities were partially dependent on variations in the CYP3A5 gene. In KTx, individuals with genotype CYP3A5 *1/*1 or *1/*3 require minor adjustments of significantly lower doses compared with the genotype CYP3A5 *3/*3, with the expression 1, which requires 1.5 to 2 times the required dose to reach target concentrations [4]. CYP3A5 genotype guided dosing allows to achieve initial target TAC concentrations promptly after transplantation, thus potentially reducing the risk of graft-rejection due to under-exposure.

CONCLUSIONS: This study shows that cooperation between nephrology, clinical pharmacology and genetics may optimize the therapy with TAC to achieve faster CT and reduce the risk of rejection and welfare cost.