PHARMACOGENETICS PROFILING OF TRANSPLANTED PATIENTS TAKING TACROLIMUS REVEALS THAT ALLELIC MUTATIONS HAVE A STRONG CORRELATION WITH ALTERED PLASMA LEVELS

Giovanni Pallio[1], Alessandra Bitto[1], Ietteria Minutoli[1], Natasha Irrera[1], Federica Mannino[1], Domenica Altavilla[2], Vincenzo Arcoraci[1], Michelangelo Rottura[1], Francesco Squadrito[1]

[1]Dep. of Clinical and Experimental Medicine, University of Messina, Messina, Italy, Messina - Italy, [2]Dep. of Biomedical and Dental Sciences and Morphofunctional Imaging, University of Messina, Messina, Italy, Messina - Italy

Introduction: The introduction of tacrolimus treatment into clinical practice improved patient survival after organ transplant due to a significant reduction of rejection. However, despite the narrow therapeutic index, the elevated inter- and intra-individual pharmacokinetic variability, and severe adverse effects, there is no guideline suggesting a pharmacogenetics profiling of subjects before tacrolimus prescription. A number of studies found a close correlation between the pharmacokinetic profile of tacrolimus and the clinical outcome. Nevertheless, despite the long-time use of the drug in clinical practice, the best way to use tacrolimus is still a matter of intense debate. For all the above reasons, therapeutic drug monitoring (TDM) is strongly suggested, but a wide proportion of patients results out of range. The aim of this study was to analyze tacrolimus levels in patients with kidney or liver transplant and to investigate the presence of genetic polymorphisms that can modify the pharmacokinetics of tacrolimus.

Material and methods: All patients with kidney, or liver graft, admitted to the Therapeutic Drug Monitoring Unit of the A.O.U. "G. Martino" of Messina, were involved for the analysis. Tacrolimus plasma levels were assayed using the Siemens Dimension EXL 200. Genomic DNA was isolated from whole blood according to the standard protocol. Primers were chosen using a common forward primer and two allele-specific reverse primers with the 3' base of each reverse primer corresponding to either wild type or mutant allele, respectively. The studied polymorphisms were: CYP3A5*1(G6986A), CYP3A4*1B (A392G) ABCB1(C3435T; C1236T; G2677A; G2677T), SLCO1B1(T521C), CYP3A4*22. Patients were stratified into 5groups according to allelic mutations: mutations that reduce tacrolimus metabolism (RM), that increase metabolism (IM), mutations on transporters (TM), mutations in all genes (AM), or without mutations (Wild Type, WT). Multivariate log-linear generalized models were used to assess the probability of being out of range, and B with 95% confidence intervals (CIs) were calculated for each covariate of interest. A $p<0.05$was considered statistically significant.

Results: A total of 79patients (64adults and 15children; 27females and 52males) with kidney (52), or liver (27) transplant, were enrolled. RM patients showed median tacrolimus plasma levels of 5.1(95%CI 4.0-6.5) taking a dose of 2.0 mg/die (95%CI 2.0-2.5); IM had tacrolimus plasma levels of 5.2(95%CI 4.4-6.1) with a median dose of 3.0 mg/die (95%CI 2.5-4.0); TM) had tacrolimus plasma levels of 5.3(95%CI 4.0-6.9) taking 1.5mg/die (95%CI 1.0-4.0); AM) showed tacrolimus plasma levels of 4.6(95%CI 2.8-6.2) taking 5.5mg/die (95%CI 3.3-7.0); while WT subjects had tacrolimus plasma levels of 5.0 (95%CI 4.6-5.8) taking 3.0 mg/die (95%CI 2.5-4.0). No differences in tacrolimus dose and plasma levels were found between groups. However, the factors that influenced dosing were age of patients ($p=0.048$) and organ graft ($p<0.001$). Considering the out of range values, an increased probability of being out of range was identified for children ($p=0.021$), RM ($p=0.041$) and AM ($p=0.046$) patients, compared to WT.

Discussion and conclusion: Our research suggest that transplanted patients have a high variability in tacrolimus levels and this variability may be also related to genetic polymorphisms. For the above mentioned reasons these data suggest that genotyping should become a standard practice before tacrolimus prescription to reduce side effects, increase efficacy, and reduce the costs for the national health system.