SOCIETÀ ITALIANA DI FARMACOLOGIA

MODELLO PER INVIO RELAZIONE DI METÀ E FINE PERIODO

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TIPOLOGIA DI BORSA RICEVUTA: Borsa SIF per brevi periodi all'estero

TIPOLOGIA DI RELAZIONE (es.: metà periodo o finale): Metà periodo

TITOLO DELLA RELAZIONE: Evaluation of genetic polymorphisms and differences in tacrolimus blood levels in transplant patients

RELAZIONE: Tacrolimus is a calcineurin inhibitor widely used as an antirejection drug for patients subjected to liver or kidney transplantation. Tacrolimus is a macrolide that binds the FK binding protein 12 (FKBP-12), thus forming a complex that in turn engages calcineurin, thus preventing the dephosphorylation and nuclear translocation of nuclear factor of activated T-cells (NFAT), inhibiting IL-2 production and T-lymphocyte activation [1]. Tacrolimus use in clinical practice is complicated by its narrow therapeutic index as well as its high pharmacokinetics variability in patients. For this reason, underexposure with the consequent risk of rejection, or, overexposure with risk of toxicity may be detected. In particular, nephrotoxicity, hyperglycemia, neurotoxicity, and hypertension were observed following tacrolimus use in transplanted patients [2], indicating the need for therapeutic drug monitoring (TDM) in tacrolimus users [3]. Unfortunately, TDM does not provide information on the right dose that should be prescribed as attack dose, although it may be useful for adjusting the therapeutic regimen. Indeed, individual differences in metabolism have to be considered when selecting the right dose to reach target blood concentrations in the early phases post-transplant.

Several papers demonstrated that variations in tacrolimus pharmacokinetics among patients are related to differences and alterations in i) the genes encoding the enzymes that metabolize for CYP3A5 and CYP3A4, ii) the drug transporter ABCB1 and SLCO1B1 [4-5]. Due to these significant differences both in the expression and consequently in the function of CYP3A4, CYP3A5, ABCB1 and SLCO1B1 genes caused by SNPs, a wide pharmacogenetics approach before transplantation may be helpful to better predict tacrolimus blood concentrations, to reduce toxicity after transplantation and to further optimize the individualization of tacrolimus dosing in transplanted patients. However, very few studies have simultaneously analyzed all the complex pattern of the SNPs causing inter-individual tacrolimus variability. Therefore, the purpose of this study was to analyze some SNPs and to investigate whether they might cause out of range values and variability in tacrolimus blood concentration. During these first 3 months of my period in Liverpool the study was approved by the Ethics Committee of Liverpool University, and a total of 200 patients referring to the "Royal Liverpool University Hospital" were enrolled. Only subjects with kidney stable transplant, receiving tacrolimus by at least 6 months as a primary immunosuppressant were included in the study. Patients with other type of transplant, or in the first months of treatment after transplant, or taking other immunosuppressants were excluded.

DNA was extracted from blood samples using the Maxwell® CSC Instrument (Promega) and concentration was determined using Nanodrop spectrophotometer (Thermo Fisher). Then, patients were genotyped for the following polymorphisms: CYP3A5*1 (G6986A), CYP3A4*1B (A392G), CYP3A4*22, ABCB1 (C3435T; C1236T; G2677T/A), SLCO1B1 (T521C). A large number of patients carried more than one mutation and therefore, a stratification according to genotypes was performed, dividing patients into 5 groups: mutations that reduce (RM) or increase (IM) tacrolimus metabolism; mutations on transporters (TM), mutations in all genes (AM) and wild type (WT). Of the 75 patients so far analyzed no difference has been observed between WT and other groups in tacrolimus blood levels. The percentage of samples out of range is significantly higher in the IM (25.9%) than in the WT group (5.4%; p=0.001). Moreover, the correlation between the presence of mutations and being out of therapeutic range is related to IM group [B= 0.213 (0.041/0.384) p=0.015], whereas RM and TM patterns are not related to the increased risk of being out of therapeutic range. Therefore, only the presence of RM mutation [b= -0.513 (-0.876/-0.150) p= 0.006] is inversely related to the

administered dose. In the next 3 months to complete the study and to increase the statistical power I will genotype the remaining patients.

References:

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3. Wallemacq, P.; Armstrong, V.W.; Brunet, M., Haufroid, V., Holt, D.W.; Johnston, A.; Kuypers, D.; Le Meur, Y.; Marquet, P.; Oellerich, M.; et al. Opportunities to optimize tacrolimus therapy in solid organ transplantation: report of the European consensus conference. Ther Drug Monit. 2009,31,139-152.

4. Shuker, N.; Bouamar, R.; Weimar, W.; van Schaik, R.H.; van Gelder, T.; Hesselink, D.A. ATP-binding cassette transporters as pharmacogenetic biomarkers for kidney transplantation. Clin Chim Acta 2012,413,1326-1337.

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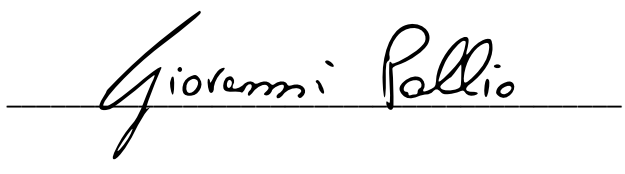
Data 22/05/2020 Firma 

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