

SIGNIFICANCE OF CYP3A5 GENE POLYMORPHISM IN SERBIAN RENAL TRANSPLANT PATIENTS

Nikola Stefanović, Tatjana Cvetković, Radmila Veličković-Radovanović, Tatjana Jevtović-Stoimenov, Dijana Stojanović and Nataša Živković

Tacrolimus (FK-506) is a part of most immunosuppressive protocols after kidney transplantation because it significantly affects the survival of transplanted organs in post-transplantation period. FK-506 is characterized by a narrow therapeutic index and large interindividual variability in pharmacokinetics. Partly, these variations can be explained by 6986A>G polymorphism CYP3A5 gene. As a substrate for CYP3A5 isoenzyme, FK-506 has a different elimination rate among individuals, which is caused by CYP3A5 gene polymorphism.

The primary objective of this study was to investigate the frequency of CYP3A5 gene polymorphism (6986A>G) in kidney transplant patients and comparison with the healthy volunteers. The second objective of this study was to determine the influence of the investigated polymorphism on FK-506 dosage regimen one month after kidney transplantation.

Pharmacogenetic retrospective study included 121 examinees - 60 patients with renal transplant and 60 healthy volunteers. Patients have routine determination of drug concentration at the Clinic of Nephrology, Clinical Center Niš, Serbia. PCR method (Ashavaid TF et al.) was used to determine the polymorphism of CYP3A5 gene.

Our study did not show statistically significant differences in allele ($p=0.616$) and genotype ($p=0.602$) frequencies between the studied polymorphism in renal transplant patients and healthy volunteers. A statistically significant difference was found between patients with different genotypes of CYP3A5 regarding dose ($p=0.001$), weight adjusted dose ($p=0.005$), and dose normalized level of FK-506 ($p=0.039$) one month after transplantation.

Patients with kidney transplant and healthy subjects in Serbian population did not show difference in the frequency of alleles of CYP3A5 gene. CYP3A5 gene polymorphism affects the dose regimen of tacrolimus one month after kidney transplantation. *Acta Medica Medianae 2013;52(1):33-38.*

Key words: tacrolimus, CYP3A5 polymorphism, pharmacogenetics, kidney transplant

University of Niš, Faculty of Medicine, Niš, Serbia

Contact: Nikola Stefanović
Faculty of Medicine Niš, Department of Pharmacology
Bulevar dr. Zorana Đinđića br. 81
18000 Niš, Serbia
E-mail: snikola84@gmail.com

Introduction

Tacrolimus (FK-506) is a part of most immunosuppressive protocols after kidney transplantation. It significantly affects the survival of transplanted organs in post-transplantation period, but also it can cause adverse effects and toxicity. Due to the narrow therapeutic index and large interindividual variability in pharmacokinetics, therapeutic drug monitoring is required in order to reduce the toxicity and improve efficiency. Consequences of both, under-immunosuppression or over-immunosuppression can be potentially severe. Under-immunosuppression increases the risk of immune-mediated rejection of transplanted organs, which

leads to potential organ loss. Otherwise, over-immunosuppression increases the risk of serious infections and malignancies, as well as a number of complications such as nephrotoxicity and post-transplantation diabetes mellitus (1-3). Cytochrome P450 3A4 (CYP3A4) and cytochrome P450 3A5 (CYP3A5) are the major enzymes in the metabolism of FK-506. Functional CYP3A4 is located in the liver and small intestine of each individual. Conversely, functionally active CYP3A5 only exists in some individuals (expressers). Otherwise, CYP3A5 is expressed in the liver, small intestine and kidney. Expresser has one of the wild-type alleles (CYP3A5*1) and may carry one of the two possible genotypes, CYP3A5*1/*1 or *1/*3. Non-expressers are homozygous for mutant allele, CYP3A5*3/*3. Differences among individuals are resulted in 6986A>G polymorphism of CYP3A5 gene, which leads to a failure in the synthesis of functional enzyme. Earlier studies have shown that CYP3A5 6986A>G polymorphism influences the pharmaco-kinetics of FK-506 (4-7). As a substrate for CYP3A5 isoenzyme, FK-506

has a different elimination rate among individuals with different pair of alleles. Almost all studies have confirmed that carriers of CYP3A5*3/*3 genotype require lower doses than carriers of CYP3A5*1/*1 or *1/*3 genotype to maintain drug level in optimal range (8-10). As the CYP3A5 is expressed within the kidneys, the primary objective of this study was to investigate the frequency of CYP3A5 gene polymorphism (6986A>G) in kidney transplant patients and comparison with the healthy volunteers. The second objective of this study was to determine the influence of the investigated polymorphism on FK-506 dosage regimen one month after kidney transplantation.

Patients and methods

Patients

Pharmacogenetic retrospective study included 121 examinees (61 patients with renal transplant and 60 healthy volunteers). Patients have routine determination of drug concentration at the Clinic of Nephrology, Clinical Center Niš, Serbia. All patients included in this study were on quaternary immunosuppressive protocol which is based on FK-506. FK-506 was introduced on the 5th day after transplantation with initial drug dose of 0.05 mg/kg/day. After the first dose, FK-506 was administered twice daily (08:00 h and 20:00 h), and the dose was adjusted according to the level of drug in the blood, in order to maintain drug level in the appropriate range (5-15 ng/ml). Besides FK-506, the patients received corticosteroid - methylprednisolone in the initial dose of 0.5 g/day, i.v., after were switched to prednisone, mycophenolate mofetil with an initial dose of 1.5 g/day and a monoclonal antibody, basiliximab in a dose of 20 mg on the 1st and 4th day after transplantation. Concentration of FK-506 in the blood was measured by immunoassay method according to the manufacturer's instructions (IMX, Abbott, Abbott Park, IL, USA).

Method for CYP3A5 gene polymorphism detection

In order to determine polymorphism in the CYP3A5 gene, we had to isolate DNA from the patients and controls. DNA was isolated from the whole blood with EDTA as an anticoagulant using Genomic DNA Purification Kit (Fermentas, Thermo Scientific, Lithuania) according to the manufacturer's instructions. Ashavaid TF et al., PCR method was used to determine the polymorphism of CYP 3A5 gene (11). Each reaction mixture in a total volume of 25 µL, contained 12.5 µL of KAPA2G Readymix (KAPA2G Readymix FastHot-Start, KapaBiosystems, Boston, USA), which already contained Hot Start DNA polymerase, dNTPs, MgCl₂ and stabilizers. In addition to the

commercial mix, we added 0.5 µL of both primers (forward and reverse, concentration of 10 pmol/µL), 10.5 µL of deionized water and 1 µL of isolated DNA (average concentration 50 ng/µL). For the amplification of PCR products, we followed the program: initial denaturation for 2 min at 95°C, followed with 35 cycles of denaturation for 15 sec at 95°C, annealing for 15 sec at 60°C, elongation for 15 sec at 72°C with final elongation for 30 sec at 72°C. Amplification products were detected on 3% agarose gel.

Statistical Data

Tables of contingency were analyzed using the Chi-square (χ^2) or Fisher test when the expected frequency was less than 5%. χ^2 -test was used to test a statistically significant difference in the frequency of alleles and genotypes between population of patients and healthy volunteers. Allele and genotype frequencies were assessed for deviation from Hardy-Weinberg equilibrium using the Fisher exact test. Doses, drug levels, and dose normalized levels between groups of patients with different genotypes were compared using T-test if the distribution was normal in the two groups. If there was a deviation from the normal distribution in the two groups, Mann - Whitney U test was performed. The value of $P < 0.05$ was considered significant. We used Statistical R software for statistical calculations. This study was approved by the Ethics Committee of the Faculty of Medicine.

Results

Demographic characteristics of the patients and controls are given in Table 1.

CYP3A5 genotypes and alleles were in Hardy-Weinberg equilibrium. The frequency of genotypes and alleles for the CYP3A5 gene in the population of patients and healthy subjects are shown in Table 2. In patient population, 10 of 61 patients (16, 39%) were heterozygous (CYP3A5 *1/*3) for the studied polymorphism, while 51 (83, 61%) patients were homozygous for the mutant type allele (CYP3A5*3/*3). Patients homozygous for the wild-type allele were not present. In the control group, 7 of 60 subjects (11.67%) were heterozygous, while 53 controls (88.33%) were homozygous (CYP3A5*3/*3). Also, we did not determine homozygous for the wild-type allele in a control population. The frequency of CYP3A5*1 allele in the patient population was 8.2%, while in the population of healthy volunteers it was 5.83%. Accordingly, the frequency of CYP3A5*3 allele was 91.8% and 94.17%, respectively. There was no statistically significant difference in allele ($\chi^2=0.517$, $p=0.616$) and genotype frequencies ($\chi^2=0.560$, $p=0.602$) of CYP3A5 gene between patients and controls.

Table 1. Demographic characteristics of the patients and controls. Age is expressed as mean \pm standard deviation

	Kidney transplant patients n=61	Healthy volunteers - controls n=60
Age (years)	39.11 \pm 10.13	40.40 \pm 11.21
Gender (male / female)	40/21	33/27
Type of transplantation (living/ cadaveric)	49/12	/

Table 2. The frequency of CYP3A5 alleles and genotypes in a population of patients and controls. Results are expressed as a number of subjects (percentage of subjects)

	Genotype		Allele	
	*1/*3	*3/*3	*1	*3
Patients	10 (16.39%)	51 (83.61%)	10 (8.20%)	112 (91.80%)
Controls	7 (11.67%)	53 (88.33%)	7 (5.83%)	113 (94.17%)

Table 3. Dose, weight-adjusted dose, level and dose-normalized level (C0/Dose) of FK-506 between patients with a different genotype for CYP3A5. Results are expressed as mean \pm standard deviation, median (interquartile range)

Genotype	*1/*3	*3/*3
Dose of FK-506 (mg / day)	11.50 \pm 4.06 [#] 12.00 (9.50 - 13.00)	7.39 \pm 3.02 7.50 (5.00 - 9.00)
Weight adjusted dose of FK-506 (mg / kg / day)	0.16 \pm 0.04 ^{##} 0.18 (0.14 - 0.18)	0.11 \pm 0.05 0.09 (0.07 - 0.13)
Level of FK-506 (ng / mL)	9.63 \pm 1.89 10.00 (7.90 - 11.35)	8.94 \pm 2.33 8.80 (7.00 - 10.90)
Dose normalized level of FK-506 (ng mL ⁻¹ / mg kg ⁻¹ day ⁻¹)	65.16 \pm 21.98 ^{###} 62.70 (51.88 - 71.98)	96.32 \pm 43.24 89.76 (61.98 - 111.82)

#: *1/*3 vs. *3/*3, p=0.001

##: *1/*3 vs. *3/*3, p=0.005

###: *1/*3 vs. *3/*3, p=0.039

Table 3 shows dose (mg/day), weight adjusted dose (mg/kg/day), level (ng/mL) and dose-normalized level (C0/Dose) of FK-506 (ng mL⁻¹/mg kg⁻¹day⁻¹) one month after renal transplantation. The obtained values were compared between groups of patients with different genotypes of CYP3A5. A statistically significant difference was found between patients with different genotypes of CYP3A5 regarding dose (p=0.001), weight-adjusted dose (p=0.005), and dose-normalized level of FK-506 (p=0.039) one month after transplantation.

Discussion

CYP3A5 gene has 11 different polymorphisms, which have been identified to date. CYP3A5 (6986A>G) polymorphism (rs776746) is most extensively studied and it is characterized by adenine (A) to guanine (G) transition at position 6986 within intron 3 of the CYP3A5 gene. Expressers (carriers of CYP3A5*1 allele) produce high level of full-length messenger RNA (mRNA), which consequently leads to high level of CYP3A5 functional protein in the body. The frequency of CYP3A5*1 allele is largely dependent on ethnic origin (7). In Caucasians, the frequency of CYP3A5*1 allele is approximately 5-15% (7), which is

consistent with our results: 8.2% in transplant patients and 5.83% in healthy volunteers. Frequency of this allele varies among other ethnic groups: in African - Americans is between 45-73%, 15% in Japanese, 27-35% in Chinese, 30% in Koreans, 25% in Mexicans and 27% in Moroccans (7-14). Hill et al., have shown that the CYP3A5*1 allele is represented with 7.9% in the population of Finns (15). Among the other Europeans, this percent was: the Greeks 5.6%, the British 6%, the Dutch 8.3% and the French 13% (16-19). The results of our study indicate that the frequency of alleles and genotypes of CYP3A5 does not differ among transplant patients and healthy volunteers, which is consistent with the research of Larriba et al. (20). This could imply that studied polymorphism does not underlie the kidney disease that consequently leads to kidney failure and organ transplantation.

Adequate immunosuppression is necessary in early period after transplantation, when there is a high risk of acute rejection of the transplanted organ. This fact with large interindividual differences in pharmacokinetics of FK-506 between individuals suggest that therapeutic drug monitoring is gaining the major importance (21,22). Recent identification of genetic polymorphism in genes that encode enzymes involved in drug

metabolism implies that genetic factors may influence interindividual variability in the pharmacokinetics of FK-506. Earlier pharmacogenetic studies have shown the impact of CYP3A5 6986A>G polymorphism on the pharmacokinetics of FK-506 (7). Also, studies have shown that carriers of CYP3A5*1 allele have a 25-40% higher clearance of FK-506, lower drug normalized levels as well as higher dose requirement to maintain an optimal level of drug, 5-15 ng/mL) (23-27). Our results suggest that the dose-and the weight-adjusted dose were affected by CYP3A5 genetic polymorphism ($p=0.001$ and $p=0.005$, respectively). These results are consistent with the results of other authors that emphasize the importance of polymorphism of CYP3A5 in the early period after transplantation (28-30). Also, we showed that carriers of CYP3A5*1 allele require higher doses of FK-506 compared to non-expressers. In addition, almost all studies have shown that CYP3A5 polymorphism affects C0/dose, C2/dose or AUC (area under the c-t curve)/dose (7,28,31-34). Our research

confirmed the results from previous studies. Serbian kidney transplant patients with CYP3A5*1 allele have C0/dose, C2/dose or AUC (area under the c-t curve)/dose.

In conclusion, patients with kidney transplant and healthy subjects in Serbian population did not show a difference in the frequency of alleles of CYP3A5 gene. CYP3A5 gene polymorphism affects the dose regimen of tacrolimus one month after kidney transplantation. Regarding this results we confirmed the importance of CYP3A5 polymorphism research in renal transplant patients. The following studies should be more involved into research of pharmacodynamics-pharmacogenetics relationship of tacrolimus as well as other drugs.

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References

- Kahan BD, Keown P, Levy GA, Johnston A. Therapeutic drug monitoring of immunosuppressant drugs in clinical practice. *Clin Ther.* 2002; 24(3): 330-50; discussion 329. [[CrossRef](#)] [[PubMed](#)]
- Press RR, de Fijter JW, Guchelaar HJ. Individualizing calcineurin inhibitor therapy in renal transplantation--current limitations and perspectives. *Curr Pharm Des.* 2010; 16(2): 176-86. [[CrossRef](#)] [[PubMed](#)]
- Velickovic-Radovanovic R, Catic-Djordjevic A, Paunovic G, Djordjevic V. Significance of therapy monitoring of immunosuppressive medicines in renal transplantation patients. *Acta Medica Medianae.* 2009; 48(2): 22 – 7.
- MacPhee IA. Pharmacogenetic biomarkers: cytochrome P450 3A5. *Clin Chim Acta.* 2012; 413(17-18): 1312-7. [[CrossRef](#)] [[PubMed](#)]
- Anglicheau D, Legendre C, Beaune P, Thervet E. Cytochrome P450 3A polymorphisms and immunosuppressive drugs: an update. *Pharmacogenomics.* 2007; 8(7): 835-49. [[CrossRef](#)] [[PubMed](#)]
- Iwasaki K. Metabolism of tacrolimus (FK506) and recent topics in clinical pharmacokinetics. *Drug Metab Pharmacokinet.* 2007; 22(5): 328-35. [[CrossRef](#)] [[PubMed](#)]
- Staatz CE, Goodman LK, Tett SE. Effect of CYP3A and ABCB1 single nucleotide polymorphisms on the pharmacokinetics and pharmacodynamics of calcineurin inhibitors: Part I. *Clin Pharmacokinet.* 2010; 49(3): 141-75. [[CrossRef](#)] [[PubMed](#)]
- MacPhee IA, Fredericks S, Mohamed M, Moreton M, Carter ND, Johnston A, et al. Tacrolimus pharmacogenetics: the CYP3A5*1 allele predicts low dose-normalized tacrolimus blood concentrations in whites and South Asians. *Transplantation.* 2005; 79(4): 499-502. [[CrossRef](#)] [[PubMed](#)]
- Ware N, MacPhee IA. Current progress in pharmacogenetics and individualized immunosuppressive drug dosing in organ transplantation. *Curr Opin Mol Ther.* 2010; 12(3): 270-83. [[PubMed](#)]
- Fredericks S, Holt DW. Pharmacogenomics of immunosuppressive drug metabolism. *Curr Opin Nephrol Hypertens.* 2003; 12(6): 607-13. [[CrossRef](#)] [[PubMed](#)]
- Ashavaid TF, Rajee HS, Shah BV, Shah SA. Design of Allele Specific PCR for Rapid Detection of CYP3A5 (A6986G) and Mdr-1 (C3435T) Polymorphisms. *Indian J Clin Biochem.* 2011; 26(1): 18-21. [[CrossRef](#)] [[PubMed](#)]
- Lamba JK, Lin YS, Schuetz EG, Thummel KE. Genetic contribution to variable human CYP3A-mediated metabolism. *Adv Drug Deliv Rev.* 2002; 54(10): 1271-94. [[CrossRef](#)] [[PubMed](#)]
- Gervasini G, Vizcaino S, Gasiba C, Carrillo JA, Benitez J. Differences in CYP3A5*3 genotype distribution and combinations with other polymorphisms between Spaniards and Other Caucasian populations. *Ther Drug Monit.* 2005; 27(6): 819-21. [[CrossRef](#)] [[PubMed](#)]
- Elmachad M, Elkabbaj D, Elkerch F, Laarabi FZ, Barkat A, Oualim Z, et al. Frequencies of CYP3A5*1/*3 variants in a Moroccan population and effect on tacrolimus daily dose requirements in renal transplant patients. *Genet Test Mol Biomarkers.* 2012; 16(6): 644-7. [[CrossRef](#)] [[PubMed](#)]
- Hilli J, Rane A, Lundgren S, Bertilsson L, Laine K. Genetic polymorphism of cytochrome P450s and P-glycoprotein in the Finnish population. *Fundam Clin Pharmacol.* 2007; 21(4): 379-86. [[CrossRef](#)] [[PubMed](#)]
- Arvanitidis K, Ragia G, Iordanidou M, Kyriaki S, Xanthi A, Tavridou A, et al. Genetic polymorphisms of drug-metabolizing enzymes CYP2D6, CYP2C9, CYP2C19 and CYP3A5 in the Greek population. *Fundam Clin Pharmacol.* 2007; 21(4): 419-26. [[CrossRef](#)] [[PubMed](#)]
- van Schaik RH, van der Heiden IP, van den Anker JN, Lindemans J. CYP3A5 variant allele frequencies in Dutch Caucasians. *Clin Chem.* 2002; 48(10): 1668-71. [[PubMed](#)]

18. King BP, Leathart JB, Mutch E, Williams FM, Daly AK. CYP3A5 phenotype-genotype correlations in a British population. *Br J Clin Pharmacol.* 2003; 55(6): 625-9. [[CrossRef](#)] [[PubMed](#)]
19. Quaranta S, Chevalier D, Bourgarel-Rey V, Allorge D, Solas C, Lo-Guidice JM, et al. Identification by single-strand conformational polymorphism analysis of known and new mutations of the CYP3A5 gene in a French population. *Toxicol Lett.* 2006; 164(2): 177-84. [[CrossRef](#)] [[PubMed](#)]
20. Larriba J, Imperiali N, Groppa R, Giordani C, Algranatti S, Redal MA. Pharmacogenetics of immunosuppressant polymorphism of CYP3A5 in renal transplant recipients. *Transplant Proc.* 2010; 42(1): 257-9. [[CrossRef](#)] [[PubMed](#)]
21. Velickovic-Radovanovic RM, Paunovic G, Mikov M, Djordjevic V, Stojanovic M, Catic-Djordjevic A, et al. Clinical pharmacokinetics of tacrolimus after the first oral administration in renal transplant recipients on triple immunosuppressive therapy. *Basic Clin Pharmacol Toxicol.* 2010; 106(6): 505-10. [[CrossRef](#)] [[PubMed](#)]
22. Velicković-Radovanović R, Mikov M, Paunović G, Djordjević V, Stojanović M, Cvetković T, et al. Gender differences in pharmacokinetics of tacrolimus and their clinical significance in kidney transplant recipients. *Gend Med.* 2011; 8(1): 23-31. [[CrossRef](#)] [[PubMed](#)]
23. Mourad M, Wallemacq P, De Meyer M, Brandt D, Van Kerkhove V, Malaise J, et al. The influence of genetic polymorphisms of cytochrome P450 3A5 and ABCB1 on starting dose- and weight-standardized tacrolimus trough concentrations after kidney transplantation in relation to renal function. *Clin Chem Lab Med.* 2006; 44(10): 1192-8. [[CrossRef](#)] [[PubMed](#)]
24. Xin-Min N, Rong G, Hong-Shan Z. Influence of CYP3A5 polymorphism on tacrolimus blood concentrations in kidney transplant patients. *J Cent South Univ Technol.* 2005; 12: 310-3.
25. Dai Y, Hebert MF, Isoherranen N, Davis CL, Marsh C, Shen DD, et al. Effect of CYP3A5 polymorphism on tacrolimus metabolic clearance in vitro. *Drug Metab Dispos.* 2006; 34(5): 836-47. [[CrossRef](#)] [[PubMed](#)]
26. Kim IW, Moon YJ, Ji E, Kim KI, Han N, Kim SJ, et al. Clinical and genetic factors affecting tacrolimus trough levels and drug-related outcomes in Korean kidney transplant recipients. *Eur J Clin Pharmacol.* 2012; 68(5): 657-69. [[CrossRef](#)] [[PubMed](#)]
27. Schiff J, Cole E, Cantarovich M. Therapeutic monitoring of calcineurin inhibitors for the nephrologist. *Clin J Am Soc Nephrol.* 2007; 2(2): 374-84. [[CrossRef](#)] [[PubMed](#)]
28. Tavira B, Coto E, Díaz-Corte C, Ortega F, Arias M, Torres A, et al. Pharmacogenetics of tacrolimus after renal transplantation: analysis of polymorphisms in genes encoding 16 drug metabolizing enzymes. *Clin Chem Lab Med.* 2011; 49(5): 825-33. [[CrossRef](#)] [[PubMed](#)]
29. Glowacki F, Lionet A, Buob D, Labalette M, Allorge D, Provôt F, et al. CYP3A5 and ABCB1 polymorphisms in donor and recipient: impact on Tacrolimus dose requirements and clinical outcome after renal transplantation. *Nephrol Dial Transplant.* 2011; 26(9): 3046-50. [[CrossRef](#)] [[PubMed](#)]
30. Tada H, Tsuchiya N, Satoh S, Kagaya H, Li Z, Sato K, et al. Impact of CYP3A5 and MDR1(ABCB1) C3435T polymorphisms on the pharmacokinetics of tacrolimus in renal transplant recipients. *Transplant Proc.* 2005; 37(4): 1730-2. [[CrossRef](#)] [[PubMed](#)]
31. Hesselink DA, van Schaik RH, van der Heiden IP, van der Werf M, Gregoor PJ, Lindemans J, et al. Genetic polymorphisms of the CYP3A4, CYP3A5, and MDR-1 genes and pharmacokinetics of the calcineurin inhibitors cyclosporine and tacrolimus. *Clin Pharmacol Ther.* 2003; 74(3): 245-54. [[CrossRef](#)] [[PubMed](#)]
32. Kuypers DR, de Jonge H, Naesens M, Lerut E, Verbeke K, Vanrenterghem Y. CYP3A5 and CYP3A4 but not MDR1 single-nucleotide polymorphisms determine long-term tacrolimus disposition and drug-related nephrotoxicity in renal recipients. *Clin Pharmacol Ther.* 2007; 82(6): 711-25. [[CrossRef](#)] [[PubMed](#)]
33. Loh PT, Lou HX, Zhao Y, Chin YM, Vathsala A. Significant impact of gene polymorphisms on tacrolimus but not cyclosporine dosing in Asian renal transplant recipients. *Transplant Proc.* 2008; 40(5): 1690-5. [[CrossRef](#)] [[PubMed](#)]
34. López-Montenegro Soria MA, Kanter Berga J, Beltrán Catalán S, Milara Payá J, Pallardó Mateu LM, Jiménez Torres NV. Genetic polymorphisms and individualized tacrolimus dosing. *Transplant Proc.* 2010; 42(8): 3031-3. [[CrossRef](#)] [[PubMed](#)]

ZNAČAJ POLIMORFIZMA CYP3A5 KOD BOLESNIKA SA TRANSPLANTIRANIM BUBREGOM U SRBIJI

Nikola Stefanović, Tatjana Cvetković, Radmila Veličković-Rađovanović, Tatjana Jevtović- Stoimenov, Dijana Stojanović i Nataša Živković

Takrolimus (FK-506) čini sastavni deo većine imunosupresivnih protokola nakon transplantacije bubrega, jer značajno utiče na preživljavanje presađenog organa u posttransplantacionom periodu. FK-506 karakteriše uzak terapijski indeks i velika interindividualna varijabilnost u farmakokinetici, koja se delimično može objasniti polimorfizmom 6986A>G CYP3A5 gena. FK-506 je supstrat za CYP3A5 izoenzim i polimorfizam CYP3A5 gena. On uslovljava razlike u brzini eliminacije ovog leka kod pojedinaca.

Primarni cilj istraživanja bio je ispitivanje učestalosti polimorfizma CYP3A5 (6986A>G) gena kod bolesnika sa transplantiranim bubregom i poređenje sa zdravim dobrovoljcima. Drugi cilj istraživanja bio je utvrđivanje uticaja ispitivanog polimorfizma na dozni režim takrolimusa mesec dana nakon transplantacije bubrega.

Retrospektivno farmakogenetičko istraživanje obuhvatilo je 121 ispitanika (61 bolesnik sa transplantiranim bubregom i 60 zdravih dobrovoljaca). Bolesnicima sa transplantiranim bubregom rutinsko određivanje koncentracije leka vršeno je na Klinici za nefrologiju Kliničkog centra Niš, Srbija. PCR metod (Ashavaid TF i sar.) korišćen je za određivanje polimorfizma CYP3A5 gena.

U našem istraživanju nije bilo statistički značajne razlike u pogledu učestalosti alela ($p=0,616$) i genotipova ($p=0,602$) ispitivanog polimorfizma između bolesnika sa transplantiranim bubregom i zdravih dobrovoljaca. Bolesnici sa različitim genotipovima za CYP3A5 statistički su se značajno razlikovali u pogledu doze ($p=0,001$), doze korigovane težinom ($p=0,005$) i nivoa korigovanog dozom ($p=0,039$) mesec dana nakon transplantacije.

Bolesnici sa transplantiranim bubregom i zdravi ispitanici u srpskoj populaciji nisu pokazali razlike u učestalosti alela CYP3A5 gena. Polimorfizam CYP3A5 gena utiče na dozni režim takrolimusa mesec dana nakon transplantacije bubrega. *Acta Medica Mediana* 2013;52(1):33-38.

Ključne reči: takrolimus, CYP3A5 polimorfizam, farmakogenetika, transplantacija bubrega