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The distribution of genetic polymorphism of CYP3A5, CYP3A4 and ABCB1 in patients subjected to renal transplantation

Distribucija polimorfizma gena koji kodiraju CYP3A5, CYP3A4 i P-glikoprotein kod bolesnika podvrgnutih transplantaciji bubrega

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Abstract

Background/Aim. Polymorphisms of genes which encode transporter P-glycoprotein and most important enzymes for tacrolimus pharmacokinetics can have significant influence reflecting on blood concentrations of this drug. The aim of this study was to examine the distribution of polymorphisms of CYP3A5, CYP3A4 and ABCB1 genes in patients subjected to renal transplantation, for the first time in our transplantation center. **Methods.** The research was designed as a prospective cross-sectional study which included 211 patients subjected to renal transplantation in the Centre for Solid Organ Transplantation of the university tertiary health care hospital, Military Medical Academy, Belgrade, Serbia. Patients of both genders, 22−69-year-old, Caucasians, subjected to immunosuppressive regimen, including tacrolimus, were recruited for the study. CYP3A5 6986A>G (the *3 or *1, rs776746), CYP3A4 -392A>G (the *1 or *1B, rs2740574) and ABCB1 3435C>T (rs1045642) genotypes were determined by TaqMan® SNP genotyping assays. **Results.** Most of our patients (94.8%) had functional CYP3A4 enzyme, while 87.7% of all the patients had diminished CYP3A5 enzymatic activity. On the other hand, about one third of them, 31.3%, had functional ABCB1 transporter. **Conclusion.** A total of 84.8% of our patients were found to express both the CYP3A5*3*3 genotype (associated with diminished CYP3A5 enzymatic activity) and CYP3A4*1*1/*1*1B (associated with functional CYP3A4 enzymatic activity), while out of all the patients with diminished CYP3A5 enzymatic activity, 68.7% had diminished activity of ABCB1 transporter. However, further studies are necessary in order to show the influence of these genetic polymorphisms on tacrolimus blood concentrations in patients after renal transplantation.

Key words:
tacrolimus; kidney transplantation; polymorphism, genetic; cyp3a4 protein, human; cyp3a5 protein, human; abcb1 protein, human.

Apstrakt

Uvod/Cilj. Polimorfizmi gena koji kodiraju transporter P-glikoprotein i najvažnije enzime za farmakokinetiku takrolimusa mogu imati značajan uticaj koji se odražava na koncentracije ovog leka u krvi. Cilj ovog ispitivanja bio je da se ispita učestalost polimorfizma gena CYP3A5, CYP3A4 i ABCB1 kod bolesnika sa transplantiranim bubregom, po prvi put u našem centru za transplantaciju. **Metode.** Urađena je prospektivna studija preseka koja je obuhvatila 211 bolesnika sa urađenom transplantacijom bubrega u Centru za transplantaciju solidnih organa Vojnomedicinske akademije u Beogradu. U studiju su bili uključeni bolesnici oba pola, starosti od 22 do 69 godina, bele rase i na imunosupresivnom režimu koji uključuje takrolimus. Urađena je genotipizacija CYP3A5 6986A>G (*3 ili *1, rs776746), CYP3A4 -392A>G (*1 ili *1B, rs2740574) i ABCB1 3435C>T (rs1045642) korišćenjem TaqMan® eseja za određivanje pojedinačnih nukleotidnih polimorfizama. **Rezultati.** Većina naših bolesnika (94,8%) imala je funkcionalan CYP3A4 enzim, dok je kod 87,7% od svih naših bolesnika CYP3A5 bio sa oštećenom aktivnošću. S druge strane, kod oko trećine (31,3%) bolesnika ABCB1 transporter bio je funkcionalan. **Zaključak.** Ukupno 84,8%

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naših bolesnika imalo je istovremeno CYP3A5*3*3 genotip, povezan sa smanjenom CYP3A5 aktivnošću, i CYP3A4*1*1/*1*1B genotip, povezan sa funkcionalnom formom CYP3A4 enzima, dok je od svih bolesnika sa smanjenom CYPA5 enzimskom aktivnošću 68,7% imalo smanjenu aktivnost ABCB1 transportera. Međutim, buduće studije su neophodne kako bi se pokazao uticaj ovih genskih polimorfizama na koncentraciju takrolimusa u krvi bolesnika nakon transplantacije bubrega.

Ključne reči:
takrolimus; transplantacija bubrega; polimorfizam, genetički; cyp3a4 protein, humani; cyp3a5 protein, humani; abcb1 protein, humani.

Introduction

Kidney transplantation presents the best way of treating patients with end-stage renal disease. The success of kidney transplantation depends on a delicate balance between the level of immunosuppression, graft rejection and occurrence of adverse effects of immunosuppressive drugs [1, 2].

Tacrolimus (Tac) is one of the most important immunosuppressive drugs which significantly improve the results of kidney transplantation [3]. However, despite its long-standing and wide applications, there are still difficulties in the optimal dosing of this drug due to significant inter- and intraindividual variability of Tac [4]. Among numerous factors that have been identified as contributors to Tac variability, bioavailability of the drug is a prominent one [5, 6]. The bioavailability may largely be due to the presence of genetic polymorphisms which are responsible for synthesis of the enzymes and transporter P-glycoprotein involved in the pharmacokinetics of the drug. It is believed that in the general population genetic is responsible for 20−95% of variability of Tac bioavailability [7]. Recently, there has been a great interest in determination of genetic polymorphisms which could predict a degree of Tac bioavailability in each patient individually [6]. Identification of genetic polymorphisms of enzymes and P-glycoprotein is a rather attractive option for individualized and efficient implementation of Tac in clinical practice. This is more important if we take into account that the genotype is stable and the immutable characteristic needs to be determined only once for a particular gene [2, 7]. Currently, the prospective clinical studies need to demonstrate if determinations of genetic polymorphisms for enzymes and the transporter involved in the pharmacokinetics of Tac before transplantation may contribute to better efficiency and safety of this drug after kidney transplantation.

Since several studies have already shown that differences in the expression of certain genes that affect Tac pharmacokinetics may result in large and unexpected variations in Tac blood concentrations in patients after the equal dose of this drug, the aim of this study was to examine the distribution of polymorphisms of CYP3A5, CYP3A4 and ABCB1 genes in patients subjected to renal transplantation, for the first time in our transplantation center.

Methods

This prospective cross-sectional study included 211 patients, 136 (64.45%) men, and 75 (35.55%) women, subjected to kidney transplantation and follow-up procedures in the Center for Transplantation of Solid Organs in the Military Medical Academy (MMA), Belgrade, Serbia. All the patients were Caucasians, aged from 22 to 69 (median 45). The patients received triple immunosuppression regimen including Tac, mycophenolate mofetil and prednisone, in usual doses [8, 9].

Informed consent was obtained from all the patients. The study was approved by the Ethics Committee of MMA (Ethical approval N° 01/31-01-13, the study protocol N° 910-1).

Peripheral blood was collected in EDTA tubes and stored at -40°C. DNA was extracted from blood by a Pure Link™ Genomic DNA Mini Kit (Invitrogen, USA) according to manufacturer's instructions.

The 211 adult patients were genotyped for single nucleotide polymorphism (SNP) of CYP3A5 at position 6986A>G (the *3 or *1, rs776746), CYP3A4 at position -392A>G (the *1 or *1B, rs2740574) and ABCB1 at exon 26 (3435C>T, rs1045642). The genotyping was detected by TaqMan® SNP genotyping assays (Life Technologies, USA) on a 7500 Real-Time PCR System (Applied Biosystems, USA).

For CYP3A4, ABCB1 and CYP3A5, the observed genotype (allele) frequencies were in Hardy-Weinberg equilibrium ($p > 0.05$).

Data statistical analysis was done using the statistical software package, IBM SPSS Statistics version 19. All variables were presented as a frequency of certain categories.

Results

In the present study, 187/211 (87.7%) patients with kidney allograft were homozygous carriers of the variant CYP3A5*3 allele. Wild type CYP3A5*1 (homozygous or heterozygous carriers) allele was found in 26/211 (12.3%) patients. The CYP3A4 genotyping showed that the majority of patients (210/211; 95.5%) had the wild type *1 allele as homozygous or heterozygous carriers of this variant. Analysis of ABCB1 showed that 66/211 (31.3%) patients were CC homozygote, 92/211 (43.6%) were CT heterozygote and 53 (25.1%) were homozygous carriers of the variant T allele. The frequencies of CYP3A5, CYP3A4 and ABCB1 genotypes are summarized in Table 1.

The results of the present study revealed that the majority of patients were found to express both CYP3A4*1*1/*1*1B genotype, associated with functional CYP3A4 enzymatic activity, and the CYP3A5*3*3 genotype, associated with diminished CYP3A5 enzymatic activity. However, six patients had both CYP3A4*1B and CYP3A5*3 genotype, associated with diminished CYP3A5 and CYP3A4 enzymatic activity (Table 2). Considering CYP3A5 and ABCB1, the majority of patients (68.7%) had diminished both CYP3A5 enzymatic activity and ABCB1 transporter activity (homozygous and heterozygous carriers of the variant T allele) (Table 3).

Table 1

Distribution of genetic polymorphisms significant for tacrolimus pharmacokinetics in the patients subjected to renal transplantation

Gene	Genotype	n (%)
CYP3A5 6986	AA (*1*1)	1 (0.5)
	AG (*1*3)	25 (11.8)
	GG (*3*3)	185 (87.7)
CYP3A4 -392	AA (*1*1)	200 (94.8)
	AG (*1*1B)	10 (4.7)
	GG (*1B*1B)	1 (0.5)
ABCB1 3435	CC	66 (31.3)
	CT	92 (43.6)
	TT	53 (25.1)

Table 2

Distribution of genetic polymorphisms encoding CYP3A4 and CYP3A5 enzymes in renal transplant recipients

Gene	Genotype	CYP3A4 -392A>G, n (%)		
		AA (*1*1)	AG (*1B)	GG (*1B)
CYP3A5 6986A>G	AA (*1*1)	1 (0.5)	-	-
	AG (*1*3)	20 (9.5)	4 (1.9)	1 (0.5)
	GG (*3*3)	179 (84.8)	6 (2.8)	-

Table 3

The distribution of genetic polymorphisms encoding enzyme CYP3A5 and transporter P-glycoprotein in the patients subjected to renal transplantation

Gene	Genotype	ABCB1 3435C>T, n (%)		
		CC	CT	TT
CYP3A5 6986A>G	AA (*1*1)	-	-	1 (0.5)
	AG (*1*3)	5 (2.4)	14 (6.6)	6 (2.8)
	GG (*3*3)	61 (31.3)	78 (43.6)	46 (25.1)

Discussion

The genes that are primarily involved in the pharmacokinetics of Tac are those encoding CYP3A family of enzymes and P-glycoprotein. Tacrolimus undergo substantial intestinal and liver metabolism after absorption from the gut lumen, and it is believed that CYP3A and P-glycoprotein are largely responsible for poor oral bioavailability of this drug [10]. The most important enzymes for Tac metabolism which belong to CYP3A family are CYP3A5 and CYP3A4. Since polymorphic CYP enzyme family is the most important system involved in Tac biotransformation, genotyping of these CYP polymorphisms provides important information that can predict its bioavailability.

While functional CYP3A4 is located in the liver and small intestine of each individual, functionally active CYP3A5 only exists in some individuals ("CYP3A5 expressers"). In our study 12.3% of patients were CYP3A5 expressers. Expressers have at least one wild-type allele (CYP3A5*1), and carry CYP3A5*1*1 or CYP3A5*1*3 genotype. On the other hand, 87.7% of our patients had CYP3A5*3*3 genotype. According to Provenzani et al. [2], it means that they are "CYP3A5 non-expressers" since they are homozygote for mutant allele CYP3A5*3. Homozygous carriers of CYP3A5*3 do not express the enzyme due to creation of a cryptic splice site [11]. Almost all studies have confirmed that carriers of CYP3A5*3*3 genotype require lower doses of Tac than carriers of CYP3A5*1*1 and CYP3A5*1*3 genotype in order to maintain drug level in optimal range [12]. On the other hand, CYP3A5*1 carriers, from all ethnic groups, had around 1.5−2 fold lower blood concentrations for a given dose of Tac than CYP3A5*3 homozygote, what could result in serious therapeutic failure and early acute rejection episodes [13]. We consider that it can be said that CYP3A5 expressers need higher Tac doses, rather that CYP3A5 non-expressers need lower doses of this drug.

Our results are also in accordance with the ones reported by other authors who have examined the frequency of this polymorphism in different ethnic groups [14]. The frequency of CYP3A5 variant alleles shows significant interethnic differences, with the wild-type CYP3A5*1 allele more common in Africans than in Caucasians and Asians [15]. Namely, percentage of non-expresser state occurs in 85% to 95% Caucasians, while in African-Americans this ratio is reversed [14]. Thus, the empirical observation that patients of African-American race required higher Tac doses in order to achieve the same blood concentration in comparison to Caucasians received its theoretical explanation [16].

CYP3A4 is the major cytochrome P450 isoform present in adult liver. There is a large inter-individual variability in hepatic CYP3A4 expression [17], since more than 20 mutations in the CYP3A4 gene have been identified, most of them with unclear clinical importance so far. Some recent studies have demonstrated that primary CYP3A4 polymorphism impli-

cated in Tac metabolism was A > G substitution at position -392 that produced variant allele referred as CYP3A4*1B with diminished enzymatic activity and reduced Tac clearance [14]. Therefore, pre-transplantation genotyping of the CYP3A4*1B, along with CYP3A5*3, could potentially bring benefit to the patients by reducing initial Tac doses among CYP3A poor metabolizers and thereby reduce the risk of reaching over therapeutic Tac concentrations [18].

Most of our patients (95.5%) were homozygous or heterozygous carriers of the variant CYP3A4*1, which were associated with the functional state of the enzyme CYP3A4. The other authors also have pointed out that enzyme CYP3A4 is predominantly active in Caucasians, in whom the presence of this polymorphism ranges from 90−98% [14, 19].

If we consider CYP3A5*3 and CYP3A4*1B polymorphism together, most of our patients (84.7%) were characterized by functional form of the CYP3A4 enzyme and diminished CYP3A5 enzymatic activity. However, since six patients had both diminished enzymatic activities of these enzymes, overexposure of them to Tac could have been expected, if the usual doses of drug were used.

Regarding ABCB1 3435C > T polymorphism alone, over 68% of patients in our study had variant T allele (CT or TT genotype), which was associated with diminished activity of P-glycoprotein. P-glycoprotein, which is encoded by the ABCB1 gene, is a large ATP-dependent transmembrane protein involved in the extracellular extrusion of many drugs, including Tac [10]. More than 700 variations in the nucleotide sequences of ABCB1 gene have been described, and some of them seem to influence the pharmacokinetics of Tac. The most extensively investigated single nucleotide polymorphisms of ABCB1 were 3435 C > T (rs1045642) in exon 26, 1236 C > T (rs128503) in exon 12, and 2677 G>T/A (rs2032582) in exon 21 [20]. It was shown that patients with wild-type genotype ABCB1 (CC) had stable Tac blood concentrations, while patients with CT or TT genotypes had up to 60% higher Tac blood levels [21]. However, many authors showed that genetic polymorphisms for P-glycoprotein *per se* had no major clinical impact on Tac metabolism, except when it existed in combination with genetic polymorphisms for CYP3A5, such as CYP3A5*3 [22]. Therefore, the effect of ABCB1 polymorphisms should be best estimated considering its association with CYP3A5 non expressers and CYP3A5 expresser's status separately [21].

Considering CYP3A5 and ABCB1 polymorphism together, most of our patients (68.7%) had CYP3A5*3*3 genotypes, associated with diminished CYP3A5 enzymatic activity, and diminished activity of ABCB1 transporter (CT or TT genotypes). Overexposure of these patients to Tac can also be expected.

In addition to these genetic polymorphisms, some authors have found that genetic polymorphisms of P450 oxidoreductase (POR) *28 and CYP3A4*22 may potentially influence Tac pharmacokinetics in patients subjected to renal transplantation [2], as well as CYP3A5 polymorphism [23].

Namely, POR is essential for the electron donation in the microsomal-CYP450-mediated mono-oxygenation, and about 40 SNPs have been identified in the POR gene [2]. POR*28 C > T mutations can increase activity of this enzyme and alter the baseline metabolic capacity of several CYP isoforms. The Tac bioavailability in patients who were CYP3A5 expressers, as well as carriers of the wild type CC POR genotype was higher than that observed in patients carrying POR allelic variants. No significant differences were observed between POR*28 CC homozygote and POR*28 T carriers in CYP3A5 non-expressers [24, 25]. Therefore, the POR genotype is important in influencing Tac metabolism only in CYP3A5 expressers.

On the other hand, CYP3A4*22 allele (rs35599367 C > T in intron 6) can also have significant influence on the Tac pharmacokinetics in renal transplant recipients [2]. The patients carrying one or two T alleles required significantly lower Tac doses comparing with the patients who were homozygous for the wild-type C allele [18, 26]. This CYP3A4*22 SNP is significantly linked to reductions in CYP3A4 mRNA production and enzyme activity in human livers [18].

Finally, it appears that CYP3A5 genotyping both in organ recipient and donor is very important for establishing personalized Tac dosage regimen. Namely, CYP3A5*3 polymorphism both in pediatric liver recipients and donors has influence on Tac dosing requirement [23]. Therefore, it was suggested that early determination of this genotype in both recipients and donors would be very helpful for adequate immunosuppressive regimen which included Tac.

Obviously, there are real expectations that genetic testing before organ transplantation can predict individual response to certain immunosuppressive drugs. This would lead to improved treatment, as well as better graft survival after renal transplantation in future.

Conclusion

The present study is the first analysis of the distribution of gene polymorphisms encoding CYP3A5, CYP3A4 and ABCB1 in patients subjected to renal transplantation in our transplantation center. A total of 84.8% of our patients were found to express both the CYP3A5*3*3 genotype, associated with diminished CYP3A5 enzymatic activity, and CYP3A4*1*1/*1*1B, associated with functional CYP3A4 enzymatic activity, while out of all the patients with diminished CYP3A5 enzymatic activity, 68.7% had diminished activity of ABCB1 transporter. However, further studies are needed which would actually show the influence of these genetic polymorphisms on Tac blood concentrations in patients after renal transplantation.

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