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EFFECT OF URIDINE DIPHOSPHATE-GLUCURONOSYLTRANSFERASE POLYMORPHISMS ON THE PLASMA CONCENTRATIONS OF MYCOPHENOLIC ACID IN TURKISH RENAL TRANSPLANT PATIENTS

TÜRK BÖBREK NAKİLLİ HASTALARDA ÜRİDİNE DİFOSFAT-GLUKURONOZİLTRANSFERAZ POLİMORFİZMLERİNİN MİKOFENOLİK ASİT'İN KAN KONSANTRASYONLARI ÜZERİNE ETKİLERİ

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ABSTRACT

Objective: The pharmacokinetics of mycophenolic acid (MPA) differ among individuals. MPA is primarily metabolized by uridine diphosphate-glucuronosyltransferase (UGT), and UGT2B7 is an important UGT for the glucuronidation of MPA. This study aimed to examine the pharmacokinetics of MPA in Turkish renal transplant patients with UGT2B7 His268Tyr (802C>T) polymorphisms.

Materials and Methods: Sixty-five renal transplants patients were included in this study. UGT2B7 (802C>T) genotyping was performed using PCR-RFLP. Concentrations of MPA were determined using a cloned enzyme donor immunoassay (CEDIA). All patients were monitored for acute rejection and graft function during the study period.

Results: The UGT2B7 (802C>T) CC, CT, and TT genotype frequencies among patients were 24 (36.9%), 36 (55.4%), and 5 (7.7%) respectively. At three and six months post-transplant respectively, levels of MPA were significantly higher in UGT2B7 (802C>T) TT carriers than in CT and CC carriers (p=0.038; p=0.021). The ratio of plasma concentration to MPA dosage for patients with 802C>T TT genotype was higher than that of CC and CT genotypes at six months post-transplant (p=0.042). Individuals carrying the TT genotype demonstrated lower dose requirements at three and six months compared with those of the CC and CT genotypes respectively (p=0.109, p=0.238). Additionally, there was no association found between UGT2B7 (802C>T) polymorphism and acute rejection (p>0.05).

Conclusion: Our results demonstrated a correlation between the UGT2B7 (802C>T) polymorphism and MPA pharmacokinetics among renal transplant patients. Determination of UGT2B7 polymorphism may be helpful for determining the optimum dose of MPA to achieve the target plasma concentration.

Keywords: Renal transplantation; pharmacogenetics; immunosuppressive therapy; polymorphism; mycophenolic acid.

ÖZET

Amaç: Mikofenolik asit'in (MPA) farmakokinetiğinde bireyler arasında farklılıklar vardır. MPA öncelikle uridin difosfat-glukuronosiltransferazlar (UGT) tarafından metabolize olur. UGT2B7, MPA glukuronidasyonu için önemli bir UGT'dir. Çalışmanın amacı, Türk böbrek nakilli hastalarda UGT2B7 His268Tyr (802C>T) polimorfizmlerinde MPA farmakokinetiğini incelemektir.

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Gereç ve Yöntem: Çalışmaya renal transplant yapılmış, 65 hasta dahil edildi. UGT2B7 His268Tyr (802C>T) genotiplemesi PCR-RFLP kullanılarak yapıldı. MPA konsantrasyonları Klonlanmış Enzim Donör Immunoassay (CEDIA) ile belirlendi. Tüm hastalar çalışma süresi boyunca akut rejeksiyon ve greft fonksiyonu açısından izlendi.
Bulgular: Hastalar arasında UGT2B7 (802C>T) CC, CT ve TT genotip frekansları sırasıyla 24 (%36,9), 36 (%55,4) ve 5 (%7,7) idi. Üçüncü ve altıncı aylarda MPA düzeyleri UGT2B7 (802C>T) TT taşıyıcılarında CT ve CC taşıyanlara göre sırasıyla istatistiksel olarak anlamlı derecede yüksek bulundu (p=0,038, p=0,021). MPA'nın doz/kan konsantrasyonu oranı nakil sonrası altıncı ayda TT genotipi taşıyanlarda CC ve CT genotipi taşıyanlara göre daha yüksekti (p=0,042). TT genotipi taşıyan bireyler sırasıyla CC ve CT genotiplerine kıyasla üçüncü ve altıncı ayda düşük doz gereksinimleri göstermişlerdir (p=0,109, p=0,238). Ayrıca UGT2B7 (802C>T) polimorfizmi ile akut rejeksiyon arasında bir ilişki bulunmamıştır (p>0,05).
Sonuç: Bizim sonuçlarımız, böbrek nakilli hastalarda UGT2B7 (802C>T) polimorfizmi ile MPA farmakokinetiği arasında bir korelasyon olduğunu göstermiştir. UGT2B7 polimorfizminin saptanması, en uygun MPA kan konsantrasyonları hedefi belirlenmesine yardımcı olabilir.
Anahtar Kelimeler: Böbrek nakli; farmakogenetik; immünsupresif tedavi; polimorfizm; mikofenolik asit.

INTRODUCTION

Renal transplantation remains the best treatment for end-stage renal disease but is associated with several complications, some of which may cause irreversible loss of graft function. Following renal transplantation, patients require permanent immunosuppressive therapy to prevent graft rejection. Successful immunosuppressive therapy affects the life of the graft (1,2). The classical triple immunosuppressive regimen involving the combined application of mycophenolate mofetil (MMF) or enteric-coated mycophenolate sodium (EC-MPS), a calcineurin inhibitor, and a steroid hormone has become well established with the continuous development of transplantation immunology in recent years (3,4). Insufficient immunosuppression might result in the rejection of transplanted organs. Excessive immunosuppression might lead to side effects such as diarrhea, anemia, leukopenia, and infection. Mycophenolic acid (MPA) is primarily metabolized by glucuronidation of the phenolic hydroxyl group by uridine diphosphate glucuronosyltransferases (UGTs) to an inactive MPA glucuronide. (5). UGTs that are involved in the metabolism of MPA include UGT1A9, UGT2B7, UGT1A8, and UGT1A7. However, a few studies have identified a series of genes that possibly contribute to the variability in MPA pharmacokinetics (6). MPA is mainly metabolized by UGT1A8 and UGT1A9 in the liver, its main metabolite being mycophenolic acid glucuronide (MPAG). However, its metabolic pathway includes another isoenzyme, UGT2B7, which generates mycophenolic acid acyl glucuronide (AcMPAG). The UGT2B7 His268Tyr (802C>T, rs7439366) polymorphism, located in exon 2, is associated with excessive exposure to the pharmacologically active acyl-glucuronide metabolite (acylMPAG) of MPA (7,8). MPA pharmacokinetics is characterized by considerable inter-and intraindividual variability. Widespread inter-patient variability in MPA pharmacokinetics was first reported in the kidney transplant population and subsequently in other transplant populations. The kinetics are thought to affect the therapeutic outcome and clinical side effects (9). MPA is relatively safe, but its gastrointestinal side effects remain a challenge for the patient's drug adherence and are a frequent cause of dose reduction or withdrawal, which may result in an increased risk of acute rejection and allograft loss (4). This study aimed to examine the impact of UGT2B7 His268Tyr (802C>T) polymorphism on the pharmacokinetics of MPA and the outcome of transplant patients.

MATERIALS AND METHODS

Patient Population and Study Protocol

A total of 65 renal transplant recipients (34 men and 31 women, ages 18-60) who underwent live kidney transplantation at İstanbul University, İstanbul Faculty of Medicine, Department of Urology, between March 2012 and January 2015 were included in this study. The median follow-up of patients who attended the clinics of nephrology in Department of Internal Medicine was 23.91±12.09 months.

Clinical Data Collection

At approximately three and six months following renal transplantation, whole blood samples (5 mL) were col-

lected from the patients by venipuncture immediately prior to and 12 h after oral MMF administration. Plasma was isolated by centrifugation at 1,900x g for 15 min and stored at -20°C until analysis.

Immunosuppressive Regimen

The eligibility criteria for the study were (1) first living-donor transplantation and (2) identical immunosuppressive regimens including tacrolimus (Prograf®, Astellas Pharma Inc., Tokyo, Japan), MMF (CellCept®, Roche Pharmaceutical, Nutley, NJ, USA), and steroids.. The renal transplant patients' weight (in kilograms) and the daily dose (in milligrams per day) of MMF for one year after transplantation were recorded; thus, dose per weight (milligrams per kilograms per day) could be calculated. The dosage adjustment was calculated by dividing each computation parameter by the dosage of MMF. In the MMF group, 1000 mg of MMF was administered twice a day. Tacrolimus was started at 0.15 mg/kg/dose and modified according to the patients' trough concentrations. Target tacrolimus concentrations were 10-15 ng/mL in the first month post-transplantation, followed by a gradual decrease of the trough concentration to 5-10 ng/mL at one year and 4-6 ng/mL thereafter. The demographic and clinical characteristics of the patients are listed in Table 1.

Determination of Plasma MPA Concentration from Whole Blood

The MPA concentration in whole blood was measured by cloned enzyme donor immunoassay (CEDIA). The CEDIA MPA Assay uses recombinant DNA technology (US Patent No. 4708929) to produce a unique homogenous enzyme immunoassay system. The assay is based on the enzyme β-galactosidase, which has been genetically engineered into two inactive fragments termed enzyme donor and enzyme acceptor. These fragments spontaneously re-associate to form fully active enzymes that, in assay format, cleave a substrate, generating a color change that can be measured spectrophotometrically (10). Na_2EDTA or K_2EDTA plasma samples were used. Specimens were labeled with the time of blood collection as well as the last drug administration. Prior to assaying patient specimens, assay calibration was performed using appropriate CEDIA MPA calibrators to generate a standard curve. The reportable range for the CEDIA MPA Assay is 0.3-10 µg/mL (11).

DNA Samples and DNA Extraction

The whole blood samples were collected in EDTA-containing tubes. Genomic DNA was extracted using a genomic DNA purification kit (Peqlab Biotechnologie GmbH, Wilmington, USA) according to a standard protocol provided by the manufacturer. DNA concentrations were determined by measuring the ratio of sample absorbance at 260 and 280 nm. The extracted DNA samples were stored at −20°C until use.

Identification of Genotypes of UGT2B7 His268Tyr (802C>T) Polymorphisms

Polymorphisms of the UGT2B7 His268Tyr (802C>T) gene were determined by polymerase chain reaction-re-

Table 1. Demographics and clinical characteristics of renal transplant patients

Parameters	
Number of patients (n)	65
Gender (female/male)	31/34
Age (years)	44.12±11.62
Body weight (kg)	60.12±10.46
Primary kidney disease (n) (%)	
Chronic glomerulonephritis	26 (20.8%)
Tubulointerstitial nephritis	4 (3.2%)
Unknown	17 (13.6%)
Primary nephrosclerosis	4 (3.2%)
Amyloidosis	3 (2.4%)
Diabetic nephropathy	9 (7.2%)
Human Leukocyte Antigen (HLA) mismatch	
0	8 (6.4%)
1–5	43 (34.4%)
≥6	12 (9.6%)
Pre HLA antibody: positive/negative	7 (14.4%)/ (85.6%)
Pre-tx creatinine (mg/dL)	7.2 4± 1.73
Post-tx creatinine (mg/dL) (month 3)	1.38±0.09
Post-tx creatinine (mg/dL) (month 6)	1.25±0.11
Acute rejection episodes n (%)	14 (21.5%)
Biopsy-proven acute rejection (n) (%)	8 (12.3%)
Clinical rejection (n) (%)	6 (9.2%)
Anti-rejection therapy (n) (%)	
Pulse steroid	8 (12.3%)
Pulse steroid + Antithymocyte globulin (ATG)	6 (9.2%)

striction fragment length polymorphism (PCR-RFLP) as described previously (7). Genotyping of UGT2B7 His268Tyr (802C>T) was performed using the following primer pair: forward 5'-TGCCTACACTATTCTA-ACC -3', reverse 5'-AGTGCAGAATTTTCAGAGA -3' (7).

Clinical variables including rejection episodes and graft function were also monitored. A rejection episode was defined based on clinical or biopsy findings according to the Banff criteria (12). Clinical rejection was identified by increased creatinine levels in the absence of infection, obstruction, or evidence of drug toxicity. Acute rejection episodes were treated with a high daily dose of 500 mg intravenous methylprednisolone for 3 days; in refractory cases with antithymocyte globulin (ATG) (2.5 to 3 mg/kg/d) for 10 to 12 days.

Ethics Statement

This study was performed according to the Declaration of Helsinki and with ethical approval from the ethics committee of the First Affiliated Hospital İstanbul University, İstanbul Faculty of Medicine (No: 2013/91). Written informed consent was obtained from all patients.

Statistical Analysis

Data analysis was carried out using the statistical package IBM Statistical Package for the Social Sciences version 21 to compute all descriptive statistics (IBM SPSS Statistics, Armonk, NY, USA). All results are expressed as the mean±SD. The Hardy-Weinberg equilibrium was tested in the frequencies of all the genotypes using a chi-square test procedure. The Kruskal-Wallis test was used for the comparison of more than two groups. Daily dose and dose-adjusted MPA plasma levels were expressed as mean ± SD. Genotype groups were compared for MPA plasma concentration and dose ratios by using a t-test for comparison between two groups. Inter-group comparisons for the UGT2B7 genotypes were performed by one-way ANOVA. The differences were accepted as statistically significant when $p<0.05$.

RESULTS

The UGT2B7 (802C>T) CC, CT, TT genotypes were detected in 24 (36.9%), 36 (55.4%) and 5 (7.7%) patients respectively. The genotypes were in Hardy-Weinberg equilibrium ($p=0.25$; $x^2=1.37$). During the follow-up period, a total of 65 episodes of gastrointestinal side effects, infections, and acute rejection events were observed in 15 patients (23.0%), 10 patients (15.4%) and 7 patients (10.8%) respectively. In a simple analysis, the presence of UGT2B7 802C>T allelic variants was insignificant for adverse events (Table 2). No statistically significant differences in serum creatinine levels were noted between UGT2B7 (802C>T) genotypes ($p>0.05$).

The plasma concentrations of MPA were significantly higher in the patients with the TT genotype three months after transplantation ($p=0.038$) when compared to patients with CT and CC genotypes. Six months post-transplantation, the ratio of plasma concentration to MPA dose for patients with the TT genotype was determined to be higher than that for patients with CC and CT genotypes ($p=0.042$).Additionally, significant differences in plasma concentrations of MPA were noted between UGT2B7 (802C>T) TT genotype versus CT and CC genotypes ($p=0.021$). The dose given to the TT genotype patients was observed to be lower than the CC and CT genotypes at three months post-transplantation, but this finding was insignificant ($p=0.108$) (Table 3).

DISCUSSION

Mycophenolic acid is widely used in combination with calcineurin inhibitors as maintenance immunosuppressive therapy for the prevention of acute and chronic rejection after transplantation (13). The clinical response to MPA shows wide interindividual variability. Due to high individual variations in pharmacokinetic parameters of MPA in renal transplant patients, plasma concentration monitoring is recommended. Many UGT-associated polymorphisms have been reported to affect UGT activity and thus affect drug metabolism (14). UGT2B7 is mainly

Table 2. The distribution of UGT2B7 CC versus CT/TT genotypes in patients with adverse events

	CC Genotype (n=24)	CT/TT Genotype (n=41)		p
Clinical outcome	n (%)	n (%)	OR (95% CI)	
Gastrointestinal side effects	9 (37.5%)	6 (14.6%)	2.00 (1.107–3.614)	0.064
Infectious	5 (9.8%)	6 (29.2%)	1.292 (0.615–2.713)	0.517
Acute rejection	5 (20.3%)	2 (4.9%)	2.180 (1.201–3.959)	0.091

involved in the glucuronidation of MPA (15). UGT2B7 (802C>T) polymorphism was reported to have a limited effect on UGT2B7 activity. However, the impact of the UGT2B7 (802C>T) allelic variant on UGT2B7 catalytic activity and also on MPA pharmacokinetics remains controversial (16). While a strong relationship between the area under the plasma concentration-time curve of MPA and the prevention of acute rejection has been reported, such correlation has not been established between pre-dose plasma concentrations of MPA and clinical outcomes (15). Pazik et al. (17) reported that in kidney transplant recipients the association between UGT2B7 802C>T polymorphism and acute rejection is limited to the early post-transplantation weeks. On the other hand, Michelon et al. (18) reported no association with UGT polymorphism and clinical outcome. In the present study, the carriers of the UGT2B7 T allele (CT/TT genotype) had a higher risk ratio of acute rejection than non-carriers (CC genotype), but this polymorphism is not significantly associated with acute rejection. Woillard et al. reported that the patients carrying the UGT1A8*2 allele had a lower risk of diarrhea than homozygous wild-type carriers. However, the study showed that this polymorphism was not related to gastrointestinal side effects (19). Pazik et al. (17) have not found any association between UGT2B7 (802C>T) polymorphism and clinical outcomes such as leukemia, infection, or diarrhea. In our study, we also found that UGT2B7 (802C>T) polymorphism was not associated with infection and gastrointestinal side effects. The large intraindividual variations in the pharmacokinetics of MPA are characterized by considerable differences in MPA plasma concentrations. Insufficient immunosuppression may result in the rejection and graft loss of transplanted organs. Excessive immunosuppression may lead to side effects such as diarrhea, anemia, and infection. It is important to understand the factors that cause these large pharmacokinetic variations in order to achieve the necessary MPA plasma concentrations (20). UGTs that are involved in the metabolism of MPA include UGT1A8, UGT1A9, UGT1A7, and UGT2B7. UGT1A9 and UGT2B7 are the principal enzymes responsible for MPAG (21). UGT-associated polymorphisms have been shown to affect UGT activity and thus affect drug metabolism. One of these, UGT2B7 (802 C>T) polymorphism, was reported to have a limited effect on UGT2B7 activity (22). Xiao-Chun et al. (20) reported that the UGT2B7+985A>G, UGT1A9-440C>T/-331T>C/-1818C>T, UGT1A8*2, and UGT1A7-622T>C polymorphisms were associated with MPA pharmacokinetics in Chinese renal transplant patients. They showed that patients who carry the UGT2B7 IVS1+985AG genotype might be

Table 3. Pharmacokinetic parameters of MPA in UGT2B7 (802C>T) genotype groups

	UGT2B7 CC	UGT2B7 CT	UGT2B7 TT	p
Patients number (n)	24	36	5	
Sex (Female/Male)	13/11	16/20	2/3	0.649
Age (years)	43.11±11.07	44.13±9.48	44.29±11.26	0.764
Weight (kg)	62.19±10.98	59.17±11.96	62.38±9.79	0.847
Third month				
MPA daily dose (mg/kg/day)	32.16±4.89	33.80±5.98	31.15±5.49	0.109
MPA plasma concentration (pg/mL)	5.2±2.7	5.1±2.2	5.6±2.4*	0.038
Plasma concentration/Dose (pg/mL/per mg/kg)	0.16±0.03	0.15±0.02	0.17±0.05	0.428
Serum creatinine (mg/dL)	1.38±0.36	1.36±0.38	1.41±0.41	0.781
Sixth month				
MPA daily dose (mg/kg/day)	31.08±3.76	31.12±4.56	29.12±4.36	0.238
MPA plasma concentration (pg/mL)	4.9±2.6	4.9±3.0	5.6±2.7*	0.021
Plasmaconcentration/Dose (pg/mL /per mg/kg)	0.15±1.88	0.15±2.28	0.19±2.18*	0.042
Serum creatinine (mg/dL)	1.26±0.42	1.21±0.38	1.29±0.36	0.617

Data are mean ± SD

*A value of $p<0.05$ was statistically significant

at a greater risk of a higher dose-adjusted MPA area under the curve (AUC). However, Kagaya et al. (23) reported that the dose-adjusted trough levels of MPA in recipients with UGT2B7*1/*1 tended to be higher than those with UGT2B7**2/*2*. Therefore, they showed that renal MPA glucuronidation might be influenced by UGT2B7 polymorphisms. Xie et al. (20) have demonstrated that *UGT2B7* IVS1+985A>G, *UGT1A9* −440C>T/−331T>C, −1818C>T, *UGT1A8*2*, and *UGT1A7* -622T>C polymorphisms were associated with the pharmacokinetics of MPA in Chinese renal transplant patients. In their research, the IVS1+985AG genotype was found to be associated with an elevated dose-adjusted MPA $AUC_{0\text{-}12\ h}$ (p=0.002), which could explain 11.2% of the interindividual variations in MPA pharmacokinetics.

Our results also showed that polymorphism of UGT2B7 (802C>T) could influence the pharmacokinetic parameters in different post-transplant periods in Turkish renal transplant patients. In this study, the UGT2B7 (802C>T) affected the dose-adjusted through plasma concentration of MPA during the post-transplantation period. However, our results showed that MPA daily doses were lower in the patients with TT mutant genotype at three and six months after transplantation. On the other hand, Bernard et al. (21) reported that there were no significant differences in either daytime and nighttime pharmacokinetics of MPA among UGT2B7*1/*1,*1/*2 and *2/*2 genotype groups. Yu et al. (24) studied pharmacokinetic data for MPA and covariate information that was retrospectively collected from 118 patients. They reported that the pharmacokinetics of MPA was best described by a two-compartment model with a first-order absorption rate with no lag time. Body weight and serum creatinine level were positively correlated with apparent clearance (CL/F). Also, they concluded that the UGT2B7 polymorphism significantly explained the interindividual variability in the initial volume of distribution.

In our study, we also found that the plasma concentrations of MPA were significantly higher in the patients with TT genotype at three and six months after transplantation when compared to patients with CT and CC genotypes.

The clinical impact of UGT2B7 on the pharmacokinetics of MPA remains unclear. MPA area below the target therapeutic window increases the risk of adverse effects such as infection, anemia, and diarrhea (25). However, patients are at an increased risk of insufficient immunosuppression and acute rejection episodes. These facts heighten the necessity of therapeutic drug monitoring because novel regimens increase the risk of inadequate or excessive immunosuppression (25).

CONCLUSION

This study highlighted functional polymorphisms in UGT2B7 (802C>T) that may be important factors of MPA pharmacokinetics. Future pharmacokinetic studies involving both genetic and clinical factors may be useful in determining the appropriate dose of MPA after organ transplantation.

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