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# Polymorphism in the P-glycoprotein drug transporter MDR1 gene in renal transplant patients treated with cyclosporin A in a Polish population

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**Abstract:**
P-glycoprotein (P-gp), the product of MDR1 gene, is a protein which mediates transmembrane transport of a great number of xenobiotics including cyclosporin A used as an immunosuppressive drug in patients with allogenic kidney grafts. The P-gp activity and expression is dependent on the MDR1 gene polymorphism in position C3435T of exon 26. In this study, C3435T polymorphism was analyzed in 116 patients with allogenic kidney graft treated with cyclosporin A and 144 randomly selected healthy individuals. The prevalence of MDR1 gene genotypes 3435CC, 3435CT, 3435TT were also compared in patients after allogenic kidney graft with both acute and chronic graft rejection (48 patients with acute and 76 with chronic graft rejection) and control groups (respectively 139 and 112). The results of the study demonstrated that the allelic frequency and MDR1 genotype distribution were similar in all evaluated groups. It was revealed that MDR1 gene polymorphism was not a predisposing factor for terminal kidney failure leading to renal transplantation. Moreover, evaluation of C3435T polymorphism of MDR1 gene will probably not be useful for characterization of groups of patients at increased risk of acute and chronic kidney graft rejection.

**Key words:**
MDR1 gene, P-glycoprotein, polymorphism, renal transplantation

## Introduction

MDR1 gene encodes P-glycoprotein (P-gp) and belongs to the family of ABC transporter proteins, which are linked with ATP and take part in transmembrane transport of many hydrophobic, cationic, amphoteric substances as well as xenobiotics [11]. P-gp is located in many organs and tissues among others in apical brush border of luminal cells of digestive system, proximal renal tubules, and hemopoetic cells [11, 20]. The tissue distribution suggests that P-gp plays a role in excreting toxic xenobiotics and metabolites.

Recently, single nucleotide polymorphisms (SNPs) of MDR1 gene have been identified, including one possessing a functional role, which is localized in a position C3435T of exon 26 [7]. In homozygous TT-allele subjects, the P-gp expression in digestive system is lower in comparison with heterozygous CT and homozygous non-mutated CC cases. Mutated ho-

mozygotes have been reported to have higher plasma concentrations of digoxin (a substrate for P-gp), which was brought about by the lack of active P-gp form in the digestive tract [7]. SNPs in MDR1 gene may alter the physiological protective role of P-gp and together with environmental factors may play an important role in the pathogenesis of some diseases, such as Parkinson's disease, ulcerative colitis, renal epithelial tumor, childhood ALL, nortriptyline-induced postural hypotension and others [3, 16, 18, 21–23].

It has been demonstrated that cyclosporin A absorption is inversely correlated with P-gp expression in digestive tract. In the distal parts of the colon, where P-gp expression is the highest, the lowest cyclosporin A absorption is observed, whereas in small intestine where P-glycoprotein expression is the lowest cyclosporin A absorption is the highest [11]. It has also been demonstrated that P-gp regulates penetration of some drugs to target cells, which seems to affect their clinical efficacy. The glycoprotein expressed on T lymphocytes, i.e. target cells for cyclosporin A, limits its intracellular concentration by extruding the drug from the cells. Thus, high activity of P-gp on the surface of T lymphocytes may be related to reduced immunosuppressive efficacy of cyclosporin A. Furthermore, P-gp can play a role in cytotoxic activity of T lymphocytes by decreasing interleukin-2 release from the activated cells [17]. Other types of cells, which are involved in allogenic graft rejection also express P-gp. Hitzl et al. proved that in NK $CD56^+$ cells, P-gp mRNA level and P-gp activity were correlated with MDR1 gene polymorphism [6]. NK cells isolated from patients with wild C/C allele of MDR1 gene are characterized by elevated P-gp mRNA levels associated with the increased P-gp activity in comparison with homozygous T/T mutated allele. Thus, immunosuppressive effects of cyclosporin A may depend not only on its blood concentration, but also on the drug levels in the target cells, where activity of P-gp may play a crucial role. So, polymorphism in MDR1 gene encoding P-gp may be an important modulator of clinical efficacy of cyclosporin A, but also a pathogenetic factor predisposing to terminal renal failure requiring transplantation.

The aim of the present study was to evaluate MDR1 allele and genotype distribution in patients with allogenic kidney transplants and healthy population as well as to evaluate the influence of C3435T polymorphism of MDR1 gene in exon 26 on the prevalence of acute and chronic rejection of the kidney grafts in patients treated with cyclosporin A.

## Experimental protocol

### Study population

Patients of Polish origin from the Pomeranian region were included in the study after giving informed consent. The protocol of the study was approved by the Ethics Committee of the Pomeranian Medical University, Szczecin, Poland. All the patients were treated with cyclosporin A as the main immunosuppressive drug. Mean cyclosporin A dosage and concentration were similar in all respective groups of the study (data not shown). Apart from cyclosporin, patients were medicated with azathioprine or scarcely with mofetil mycophenolate as well as verapamil, diltiazem and prednisone depending on their status after transplantation. Patients who were included in the study were divided into the following groups (study groups were marked with letter "A" and control ones with letter "B").

Group 1A consisted of 48 patients diagnosed with acute graft rejection (28 males, 20 females) aged from 16 to 62 years (mean 44.5 ± 11.2 years). The diagnosis of acute kidney graft rejection was based on the following criteria: time after transplantation 3–360 days, graft tenderness, 10–25% increase in serum creatinine concentration within 1 to 2 days in reference to the initial concentration, which might be accompanied by urine retention, temperature increase over 38°C [24]. The clinical diagnosis of acute graft rejection was confirmed by kidney biopsy in a majority of cases. Group 1B contained 139 posttransplant patients without symptoms of acute graft rejection (80 males, 59 females) aged 19 to 72 years (mean 44.1 ± 11.1 years).

Group 2A consisted of 76 patients diagnosed with chronic graft rejection (42 males, 34 females) aged between 19 and 72 years (mean 45.1 ± 10.8 years). The diagnosis of chronic kidney graft rejection was based on the clinical symptoms (gradual deterioration of kidney function and reduced diuresis), biochemical tests (increase in urea and creatinine serum level) and imaging tests, in some cases also renal biopsy. Group 2B contained 112 posttransplant patients without

symptoms of chronic graft rejection (66 males, 46 females) aged from 16 to 69 years (mean 43.3 ± 11.3 years).

A total of 116 unrelated, otherwise healthy posttransplant kidney patients (66 males, 50 females) aged from 21 to 72 years (mean 42.29 ± 11.29 years) were enrolled into the group 3A. Control samples (group 3B) were derived from 144 randomly selected healthy individuals (70 males, 74 females), aged from 19 to 93 years (mean 66.28 ± 17.65 years). Allocation of patients into a specific study group was based on clinical picture, and in some cases patients were ascribed to two study groups depending on their characteristics.

### Genotyping

Genomic DNA was extracted manually (precipitation with trimethylammonium bromide salts from leukocytes contained in 450 μl of venous blood with ethylenediaminetetraacetic acid as an anticoagulant) [5]. DNA was then precipitated in 95% ethanol, dissolved in distilled water and stored at –20°C until analysis. MDR1 C3435T mutation was determined using the polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) assay [3]. A 197-bp fragment of exon 26 was amplified from genomic DNA with the primer pair P1 and P2. The primer sequences were: P1 (sense): 5'-TGTTTTCAGCTGCTTGATGG-3'; P2 (antisense): 5'-AAGGCATGTATGTTGGCCTC-3'. PCR amplification was performed in a total volume of 100 μl that contained 200 ng of genomic DNA (dATP, dCTP, dGDP and dTTP, 200 μmol/l each, MBI fermantas, Vilnius, Lithuania), 250 ng of each primer; 1.5 mmol/l magnesium chloride, and 2U *Taq* DNA polymerase (Gibco BRL Life Technologies, Glasgow, Scotland). The amplification reaction was performed using the Mastercycler 5330 (Eppendorf). PCR amplification consisted of an initial denaturation for 2 min at 94°C, followed by 35 cycles of denaturation at 94°C for 30 s, annealing at 60°C for 30 s, and extension at 72°C for 30 s. The terminal elongation was performed at 72°C for 7 min. In an amplified 197 bp fragment the C3435T polymorphism affects a restriction enzyme cleavage site for *Sau3*AI in such a way that after digestion with this enzyme for 16 h at 37°C, the 3435-C allele can be detected by the presence of two fragments, which are 158 bp and 39 bp long. The presence of 3435-T allele in the amplified segment remaining uncut, and the presence of a heterozygous genotype results in the presence of all three bands. DNA fragments generated after restriction enzyme digestion were separated on a 3.5% agarose gel. Restriction fragments were visualized after ethidium bromide staining of the agarose gel with the use of an ultraviolet transilluminator.

### Statistical analysis

Frequencies of genotypes and alleles were given with their 95% confidence intervals (95% CI). The distribution of genotypes in kidney transplant patients was compared with healthy subjects and statistically evaluated by the use of the $\chi^2$ test with Yate's correction for small groups (Epi Info 6 program, version 6.2, World Health Organization, Geneva, Switzerland).

## Results and Discussion

The study involved analysis of MDR1 gene C3435T polymorphism of exon 26 in patients after allogenic kidney graft, treated with cyclosporin A in comparison with MDR1 polymorphisms in healthy population. The prevalence of MDR1 gene genotypes 3435CC, 3435CT, 3435TT was also compared in patients after allogenic kidney graft with both acute and chronic graft rejection and respective control groups. The study assumed that C3435T mutations of MDR1 gene may also be one of the reasons of terminal renal failure by influencing P-gp activity. The differences in MDR1 genotype frequency in healthy population and in subjects with terminal renal insufficiency might be the factor predisposing to the development of the disease, including those originating in the kidney. Siegsmund et al. observed higher T allele prevalence in patients with kidney cancer [23]. Moreover, it was shown that African population is characterized by low T allele frequency which may determine statistically rarer occurrence of renal epithelial tumors, especially non-clear cell renal carcinoma prevalence, than in other populations [12]. The aforementioned reports have proved that C3435T polymorphism in exon 26 of MDR1 gene may underlay development of some diseases by modulation of P-gp expression.

The aim of this study was to evaluate MDR1 gene polymorphism in posttransplant kidney patients with acute and chronic graft rejection as well as posttrans-

**Tab. 1.** Characteristics of the study patients

| Parameter | Group | | | | | | Statistical significance |
|---|---|---|---|---|---|---|---|
| | 1A | 1B | 2A | 2B | 3A | 3B | |
| | mean ± SD | | | | | | |
| Age (years) | 44.5 ± 11.2 | 44.1 ± 11.1 | 45.1 ± 10.8 | 43.3 ± 11.3 | 44.0 ± 11.1 | 63.1 ± 17.5 | n.s. |
| Age at the moment of renal transplantation (years) | 42.5 ± 11.3 | 38.5 ± 11.6 | 38.6 ± 11.2 | 39.8 ± 12.0 | 39.2 ± 11.6 | – | $p < 0.05$ for 1A/1B |
| Renal donor age (years) | 49.2 ± 12.3 | 41.6 ± 13.4 | 40.8 ± 12.3 | 45.0 ± 14.2 | 43.6 ± 13.1 | – | $p < 0.0007$ for 1A/1B |
| Grade of graft compatibility (points) | 12.3 ± 3.1 | 12.9 ± 3.5 | 12.5 ± 3.2 | 12.9 ± 3.6 | 12.7 ± 3.4 | – | n.s. |
| Time of cold ischemia (h) | 20.7 ± 8.5 | 16.9 ± 8.3 | 21.5 ± 9.8 | 18.0 ± 6.5 | 20.0 ± 7.9 | – | $p < 0.008$ for 1A/1B<br>$p < 0.007$ for 2A/2B |
| Creatinine (mg%) | 5.84 ± 3.1 | 2.78 ± 1.6 | 3.5 ± 1.7 | 2.65 ± 0.73 | 2.74 ± 2.2 | 0.93 ± 2.1 | $p < 0.000001$ for 1A/1B<br>$p < 0.000001$ for 2A/2B<br>$p < 0.000001$ for 3A/3B |
| Urea (mg%) | 151.2 ± 62.5 | 65.2 ± 38.8 | 65.1 ± 35.8 | 54.4 ± 27.0 | 87.8 ± 58.8 | 29.68 ± 8.4 | $p < 0.000001$ for 1A/1B<br>$p < 0.04$ for 2A/2B<br>$p < 0.04$ for 3A/3B |
| | n (%) | | | | | | |
| Early dialysis | 22 (45.8) | 45 (3.4) | 26 (34.2) | 40 (35.7) | – | – | n.s. |

n.s. – non significant ($p > 0.05$)

plant patients without complications and healthy controls. The characteristics of studied subjects including age, age at the moment of renal transplantation, renal donor age, grade of graft compatibility, time of cold ischemia, urea, creatinine, bilirubin, aspartate transaminase (AST), alanine transaminase (ALT) levels (liver test results not shown), early dialysis are presented in Table 1. Statistically significant differences of serum creatinine and urea levels were noted between group 1A *vs*. group 1B patients, i.e. 5.84 ± 3.1 mg/dl and 151.2 ± 62.5 mg/dl *vs*. 2.78 ± 1.6 mg/dl and 65.2 ± 38.8 mg/dl ($p < 0.000001$ and $p < 0.000001$, respectively), between group 2A *vs*. group 2B patients, i.e. 3.5 ± 1.7 mg/dl and 65.1 ± 35.8 mg/dl *vs*. 2.65 ± 0.73 mg/dl and 54.4 ± 27.0 mg/dl ($p < 0.0000001$ and $p < 0.04$, respectively), and between group 3A *vs*. healthy controls: 2.74 ± 2.2 mg/dl and 87.8 ± 58.8 mg/dl *vs*. 0.93 ± 0.21 mg/dl and 29.68 ± 8.4 mg/dl ($p < 0.000001$ and $p < 0.00001$, respectively). There were statistically significant differences in age at the moment of renal transplantation and renal donor age in the group 1A *vs*. group 1B patients, i.e. 42.5 ± 11.3 years and 49.2 ± 12.3 years vs. 38.5 ± 11.6 years and 41.6 ± 13.4 years ($p < 0.05$ and $p < 0.0007$), respectively. Statistically significant differences in time of cold ischemia between group 1A *vs*. 1B patients, i.e. 20.7 ± 8.5 hours *vs*. 16.9 ± 8.3 hours ($p < 0.008$), respectively, between group 2A *vs*. group 2B patients, i.e. 21.5 ± 9.8 hours *vs*. 18.0 ± 6.5 hours ($p < 0.007$), respectively were also observed. All other parameters evaluated, such as age, grade of graft compatibility, bilirubin serum concentrations, AST, ALT serum activities and early dialysis did not differ markedly in all studied subjects.

The distributions of MDR1 allele and genotypes in allogenic kidney transplant patients and healthy population are shown in Table 2. The study and the control groups were characterized by similar distribution of MDR1 genotypes. There were no significant differences in the frequency of 3435CC, 3435CT and

**Tab. 2.** The distribution of MDR1 allele and genotypes in posttransplant patients with (1A) and without (1B) acute graft rejection, in posttransplant patients with (2B) and without (2A) chronic graft rejection as well as in allogenic kidney graft patients (3A) and in healthy population (3B)

| Genotype | Group 1A (n = 48) | | Group 1B (n = 139) | | p value |
|---|---|---|---|---|---|
| | n (%) | 95% CI | n (%) | 95% CI | |
| 3435CC | 9 (18.7) | 8.9–32.6 | 29 (20.9) | 14.9–28.4 | 0.75 |
| 3435CT | 27 (56.3) | 41.2–70.5 | 78 (56.1) | 47.8–64.1 | 0.98 |
| 3435TT | 12 (25.0) | 13.6–39.6 | 32 (23.0) | 16.8–30.7 | 0.78 |
| | Group 2A (n = 76) | | Group 2B (n = 112) | | |
| 3435CC | 18 (23.7) | 14.7–34.8 | 20 (17.9) | 11.9–26.0 | 0.32 |
| 3435CT | 40 (52.6) | 40.8–64.2 | 65 (58.0) | 48.8–66.8 | 0.46 |
| 3435TT | 18 (23.7) | 14.7–34.8 | 27 (24.1) | 17.1–32.8 | 0.94 |
| | Group 3A (n = 116) | | Group 3B (n = 144) | | |
| 3435CC | 21 (18.10) | 11.09–25.11 | 31 (21.53) | 14.82–28.24 | 0.49 |
| 3435CT | 70 (60.35) | 51.45–69.25 | 75 (52.08) | 45.37–58.79 | 0.30 |
| 3435TT | 25 (21.55) | 14.07–29.03 | 38 (26.39) | 19.19–33.59 | 0.37 |

3435TT genotypes between patients after allogenic kidney transplantation and healthy volunteers. The observed lack of differences in the genotypes distribution may be partly ascribed to inhomogeneous etiology of renal insufficiency (diabetes, glomerulopathies, hypertension, etc.). The frequency of alleles and distribution of MDR1 gene genotypes from the present study are similar to other European populations, e.g. German population [2] and differ from West Africans (3435CC frequency 83%), African Americans (3435CC – 61%) and Japanese population (3435CC – 36%) [19]. Another group of Polish population recruited from the central region of Poland had higher frequency of 3435CC (42%) genotypes [8].

Genetic variability may also influence pharmacokinetics of drugs and directly modulate their pharmacodynamic features. Due to similar P-gp distribution to general population, the efficacy of cyclosporin A treatment in renal transplant patients is not compromised by MDR1 gene polymorphism and the glycoprotein activity. Lown et al. revealed an association between low bioavailability of cyclosporin A in patients after renal transplantation and high P-gp expression in the gastrointestinal system [13]. Similar results were obtained by Masuda et al. in small intestine recipients who were administered cyclosporin A and tacrolimus [15]. Intestinal absorption of cyclosporin A may then be dependant on P-gp expression and MDR1 gene polymorphism. Yates et al. reported that patients bearing at least one T allele were characterized by increased bioavailability of cyclosporin A in comparison with homozygous patients having two allele in position 3435 [26]. Furthermore, in mutated TT homozygous patients the therapeutic blood concentration of cyclosporin A was achieved after oral administration of lower doses of the drug than in patients with two wild-type C allele. Those data suggest that the presence of the mutated T allele is associated with lower intestinal P-gp expression which leads to increased cyclosporin A bioavailability. Based on the reports that P-gp activity is genetically determined, Anglicheau et al. evaluated a relationship between cyclosporin A serum concentration and MDR1 gene polymorphism in position C3435T [1]. It was shown that patients with TT genotype were characterized by slightly higher cyclosporin A concentrations after oral administration than homozygous patients with two wild-type CC allele. However, the differences were not statistically significant. Von Ahsen et al. evaluated the effect of MDR1 gene C3435T polymorphism on dose requirements and cyclosporin A blood concentrations as well as rejection incidence in patients after renal transplantation [25]. No influence of MDR1 gene polymorphism on cyclosporin A doses needed to

maintain adequate cyclosporin A trough concentrations was found. Moreover, the investigated polymorphisms had no correlation with the incidence of acute rejection. Similar findings were reported by Mai et al., who demonstrated no effect of MDR1 haplotypes on steady-state pharmacokinetics of cyclosporin in renal transplant patients [14]. One of possible factors which might contribute to discrepancies of the reported findings is co-medication. As demonstrated by Kuzuya et al., amlodipine co-administration to cyclosporin was a predominant factor affecting pharmacokinetics of the latter drug [10]. In the present study, patients were administered verapamil and diltiazem which could have affected pharmacokinetics of cyclosporin as well as transmembrane transport of cyclosporin.

The study group with acute rejection was characterized by the following the MDR1 genotypes: 25% for 3435CC, 42% for 3435CT and 33% for 3435TT. There were no differences in the incidence of acute rejection among the above C3435T genotypes. However, in lung transplant patients, it was demonstrated that C allele of MDR1 gene, exon 26, position 3435, predisposed to persistent organ rejection, i.e. 72% of patients with the C allele had acute persistent rejection in comparison to 52% for TT patients ($p = 0.04$) [27].

The observations of the present study are in keeping with the aforementioned observations of von Ashen et al. The allele and genotype distribution in the population of acute and chronic kidney graft rejection patients was similar to transplant patients without rejection complications (Tab. 2). Similarly, no effects of MDR1 gene polymorphism on tremor and gingival hyperplasia in kidney transplant patients medicated with cyclosporin A was documented [4, 9].

Based on the results from the present study, it can be concluded that MDR1 gene polymorphism will not probably be useful in the diagnostics of higher risk of development of terminal renal failure leading to transplantation. Moreover, the evaluation of C3435T polymorphism of MDR1 gene will probably not be useful for characterization of groups of patients at increased risk of acute and chronic kidney graft rejection.

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