# Effect of Multidrug-Resistant 1 (MDR1) and CYP3A4*1B Polymorphisms on Cyclosporine-Based Immunosuppressive Therapy in Renal Transplant Patients

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**Background:** Immunosuppressive drugs such as cyclosporine A (CsA) are characterized by a narrow therapeutic range and high interindividual pharmacokinetic variations. Therefore, the effective monitoring of drug serum level is crucial for successful therapy. This variability can be caused by polymorphisms in genes encoding drug transporters and enzymes responsible for biotransformation. The aim of this study was to determine the relationship between CYP3A4*1B and MDR1 polymorphisms and dose requirements to achieve the target therapeutic range for CsA.

**Material/Method:** The study group consisted of 184 patients after kidney transplantation who were treated with immunosuppressive therapy. The MDR1 3435C>T and CYP3A4*1B polymorphisms were determined by the real-time PCR using the LightCycler® 480 device (Roche Diagnostics).

**Results:** Patients with the CYP3A4*1/*1 genotype received the lowest mean dose of CsA compared to CYP3A4*1/*1B, and had a higher average drug concentration in the blood. In the case of MDR1 3435C>T polymorphism, we observed that patients with the CC genotype received lower doses of CsA than patients with the CT and TT genotypes. Average drug concentration in the blood was comparable to individuals with different MDR-1 genotypes. Analysis of dependence between both polymorphisms and concentration/dose ratio showed no statistically significant differences.

**Conclusions:** The characterization of CYP3A4*1B and 3435C>T MDR1 polymorphism cannot provide useful guidance for individualizing CsA dosages in renal transplant patients by indicating the optimal dose of these drugs without exposing patients to possible adverse effects associated mainly with nephrotoxicity.

**MeSH Keywords:** Immunosuppression • Kidney Transplantation • Pharmacogenetics

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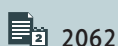
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## Background

Immunosuppressive drugs inhibit the immune response to prevent allograft rejection, but also cause immunodeficiency and produce many other adverse effects. These drugs, such as cyclosporine A (CsA), are characterized by a narrow therapeutic range and high interindividual pharmacokinetic variations. Therefore, it is essential to monitor CsA concentrations to improve the efficacy and reduce the toxicity of the drug. A level of immunosuppression that is too low may lead to graft rejection, while high levels of immunosuppressive drugs in the blood may have a toxic effect. Such variability is often caused by polymorphisms in genes encoding drug transporters and enzymes responsible for biotransformation [1–3].

CsA is substrate of both P-glycoprotein (P-gp) and cytochrome P450 3A (CYP3A). These drugs are mainly metabolized by CYP3A4 and CYP3A5, which catalyze the metabolism of structurally diverse xenobiotics and are present mainly in the human liver and small intestine [4,5]. Clinical studies have shown that a substitution in the promoter region (−392A>G) of the CYP3A4 gene leading to the creation of the mutant CYP3A4*1B allele can influence CYP3A4 expression or enzymatic activity [6,7]. In humans, the frequency of this allele varies depending on the population, ranging from 0.0% among Chinese to 54.6% among African Americans. It has also been shown that individuals with the CYP3A4*1B allele have an increased risk of prostate cancer and breast cancer [8,9].

The drug transporter P-gp is encoded by the multidrug-resistant 1 (MDR1) gene in humans and acts as a trans-membrane efflux pump involved in the export of a variety of xenobiotics. The rate of intestinal absorption of drugs acting as substrates for P-gp is correlated with several polymorphisms of the MDR1 gene [3,10,11]. The most widely studied polymorphism is the synonymous SNP 3435C>T in exon 26, where the TT homozygotes have significantly lower P-gp levels in the small intestine and the highest plasma concentrations of digoxin after oral administration [12,13].

It is postulated that the comparison of MDR1 and CYP3A4/5 polymorphisms with CsA dose may be useful as a predictor of P-gp and CYP3A4/5 activity. The aim of this study was to determine the relationship between CYP3A4*1B and MDR1 polymorphisms and dose requirements to achieve the target therapeutic range following renal transplantation in Polish patients.

## Material and Methods

The study group consisted of 184 patients after kidney transplantation who were treated with immunosuppressive therapy. The recipients requiring follow-up were recruited at the Division of Nephrology and Kidney Transplantation, Independent Public Provincial Hospital in Szczecin, and the Department of General Surgery and Transplantation, Pomeranian Medical University in Szczecin. For the present study, we selected all kidney patients treated in transplant outpatient clinic from April 2014 to December 2016, between 18 to 81 years of age, with a stable renal allograft function (there are no data indicating the occurrence of acute rejection episodes during the observation time). Children under 18 years of age were not included in the study. Also, double or previous transplants were excluded.

This study was performed in accordance with a protocol approved by the Bioethics Committee at Poznan University of Medical Sciences and Pomeranian Medical University in Szczecin. Biochemical parameters were analysed to determine the potential risk for graft rejection.

Genomic DNA was extracted from EDTA-anti-coagulated whole blood using the QIAamp DNA Blood Mini Kit (Qiagen, Germany) according to the manufacturer's protocol. DNA purity and concentration were measured by spectrophotometry (EPOCH Spectrophotometer, Biokom). The MDR1 3435C>T and CYP3A4*1B polymorphisms were determined by the real-time PCR method using the LightCycler® 480 device (Roche Diagnostics). Fluorescent dye-labelled hybridization probes were used for genotyping. The analysis of the results was based on the melting curve using LightCycler® 480 Basic Software. A set of LightSNiP rs2740574 for the CYP3A4 polymorphism and a set of LightSNiPrs1045642 for MDR1 containing appropriate concentrations of specific primers and probes for the amplified fragments were prepared according to the manufacturer's instructions.

In addition, fasting whole blood concentration of cyclosporine was determined before drug administration (C0 concentration; this is a standard procedure during follow-up). The analysis was performed using the ARCHITECT i2000SR analyzer (Abbott). The ARCHITECT System Cyclosporine (Abbott) was used to determine drug concentrations based on chemiluminescent microparticle immunoassay (CMIA). The functional sensitivity of the ARCHITECT Cyclosporine assay was designed as ≤30.0 ng/ml.

Statistical analysis was performed using SPSS version 17.0. Allele and genotype frequencies were assessed using the Pearson $\chi^2$ test. We also used the Pearson $\chi^2$ test to assess the Hardy-Weinberg equilibrium. The analysis of the clinical and biochemical parameters and their relationship with the MDR1 and CYP3A4*1B polymorphisms was conducted using one-way ANOVA (SPSS, Inc.). P values <0.05 were considered as statistically significant.

**Table 1.** Genotype and allele frequencies of the CYP3A4*1B and MDR1 polymorphisms in patients after transplantation receiving cyclosporine (CsA).

| Genotype/allele | Observed values n (%) | Expected values % |
|---|---|---|
| **CYP3A4*1B** | | |
| CYP3A4*1/*1 | 173 (94.02) | 94.11 |
| CYP3A4*1/*1B | 11 (5.98) | 5.80 |
| CYP3A4*1B/*1B | – | 0.09 |
| Total | 184 (100) | 100.00 |
| **MDR1 3435C>T** | | |
| CC | 45 (24.45) | 22.61 |
| CT | 85 (46.20) | 49.88 |
| TT | 54 (29.35) | 27.51 |
| Total | 184 (100) | 100.00 |

The expected value was calculated in accordance with the Hardy-Weinberg equilibrium.

## Results

We analysed the influence of the CYP3A4*1B and MDR1 3435C>T polymorphisms on the concentration of immuno-suppressive drugs in venous blood and the function of renal allograft. Allele and genotype frequencies of the CYP3A4*1B and MDR1 3435C>T polymorphisms in patients receiving CsA are presented in Table 1. No differences in the distribution of alleles and genotypes for the studied group were found. The frequency distribution of the genotypes was consistent with the Hardy-Weinberg equilibrium. In addition, the $\chi^2$ test did not show significant difference between the investigated groups (Table 1).

By analysing CYP3A4*1B polymorphism, we showed that patients with the CYP3A4*1/*1 genotype received lower mean doses of CsA compared to CYP3A4*1/*1B (121.50 mg/day *vs.* 184.55 mg/day, p>0.05), and had a higher average drug concentration in the blood (115.65ng/ml *vs.* 102.72 ng/ml, p>0.05). Also, we noted that patients with the CYP3A4*1/*1 genotype had lower mean body weight compared to CYP3A4*1/*1B (78.4 kg *vs.* 87.3 kg, p>0.05). However, the higher dose in patients with CYP3A4*1/*1B could be the result of increased CYP3A4 enzyme activity, considering the persistent low concentration of the drug in the blood.

In the case of MDR1 3435C>T polymorphism, we observed that patients with the CC genotype received lower doses of CsA than patients with the CT and TT genotypes (Tables 2, 3). In addition, the average drug concentration in the blood among analysed samples was comparable to individuals with different genotypes. We found no statistically significant differences between both polymorphisms and concentration/dose ratio (Table 3).

In addition, a comparison of biochemical and clinical parameters between different genotypes of the CYP3A4*1B and MDR1 3435C>T polymorphisms in patients receiving CsA showed no statistically significant differences (Tables 2, 4). We showed that factors such as age, body weight, BMI, and functional parameters of the kidneys and liver did not affect the dosage of CsA in relation to the polymorphism analysed. The patients had no episodes of acute rejection in the third month after transplantation because the presented values of the biochemical parameters such as creatinine, eGFR, and potassium after transplantation suggested a successful transplant.

## Discusion

Studies on the individualization of immunosuppressive therapy are very important in patients after renal transplantation because insufficient levels of immunosuppression can lead to acute rejection episodes, while high drug levels in the blood can cause toxicity, hyperlipidemia, hypertension, increased risk of infections, and other adverse effects.

In this study, we examined the effect of CYP3A4*1B and MDR1 3435C>T polymorphisms on dose and blood concentration of CsA, as well as the risk of acute rejection episodes. Our results indicated that patients with the CYP3A4*1/*1 genotype received lower mean doses of CsA compared to CYP3A4*1/*1B.

A similar observation was also noted by Żochowska et al., who evaluated the effects of CYP3A4*1B polymorphism on the pharmacokinetics of CsA in renal transplant recipients. Their study showed that subjects with at least 1 mutant CYP3A4*1B allele required significantly higher doses of CsA compared to those with the CYP3A*1 alleles (455.04±128.68 mg/day *vs.* 261.68±64.72 mg/day; p<0.001). They also indicated that higher doses of CsA to achieve the therapeutic concentration were correlated with a risk of increased blood pressure and developing proteinuria [1]. However, a study conducted in India (with similar numbers of patients) showed no relationship between CYP3A4 * 1B polymorphism and the pharmacokinetics of CsA [14].

There are no data available in the literature regarding variability of dose regimen over time. Such time-related variations can occur due to factors such as epigenetic changes. However, clinical practice shows that once established, the dose remains stable or varies within a very minimal range. Taking the above into consideration, we also analyzed the dependence of the investigated polymorphisms on the concentration/dose ratio.

**Table 2.** Comparison of selected clinical and biochemical parameters between the genotypes of the CYP3A4*1B polymorphism in patients receiving cyclosporine (CsA). Values normally distributed are expressed as means ± standard deviation (SD).

| Study group | CYP3A4*1/*1 wt/wt n=173 | 95% CI | CYP3A4*1/*1B wt/mt n=11 | 95% CI | P |
|---|---|---|---|---|---|
| CsA dose (mg day-1) | 121.50±61.39 | 112.28–160.71 | 184.55±51.01 | 160.27–198.82 | 0.14 |
| Concentration (C0) of CsA in the blood (ng mL-1) | 115.65±48.97 | 108.31–123.01 | 102.72±38.78 | 76.67–128.77 | 0.25 |
| Age (years) | 54.18± 12.61 | 52.29–56.07 | 49.27±12.61 | 40.80–57.74 | 0.35 |
| Weight (kg) | 78.44±16.22 | 76.00–80.88 | 87.27±28.33 | 68.24–106.31 | 0.09 |
| BMI (kg m$^2$-1) | 27.18±4.87 | 26.45–27.91 | 29.02±8.21 | 23.51–34.53 | 0.24 |
| Systolic blood pressure (mmHg) | 132.31±12.86 | 130.38–134.24 | 138.63±16.75 | 127.38–149.88 | 0.12 |
| Diastolic blood pressure (mmHg) | 82.72±8.13 | 81.49–83.93 | 84.54±11.51 | 76.82–92.27 | 0.48 |
| ALT (U L-1) | 18.98±10.41 | 17.42–20.55 | 23.73±18.19 | 11.51–35.95 | 0.16 |
| AST (U L-1) | 20.59±8.71 | 19.28–21.89 | 21.36±10.27 | 14.46–28.26 | 0.77 |
| Bilirubin (mg dL-1) | 0.61±0.29 | 0.56–0.65 | 0.57±0.26 | 0.41–0.75 | 0.71 |
| Total cholesterol (mg dL-1) | 187.91±38.87 | 181.95–193.87 | 195.18±49.07 | 162.21–228.15 | 0.55 |
| Cholesterol-HDL (mg dL-1) | 62.97±20.78 | 59.16–66.80 | 63.80±18.36 | 44.53–83.07 | 0.92 |
| Cholesterol-LDL (mg dL-1) | 94.85±34.37 | 88.51–101.21 | 116.83±60.69 | 53.14–180.53 | 0.14 |
| Triglycerides (mg dL-1) | 141.97±65.69 | 129.88–154.05 | 151.17±60.22 | 87.96–214.36 | 0.74 |
| Total lipids (mg dL-1) | 636.19±129.69 | 612.34–660.04 | 700.50±191.41 | 499.63–901.37 | 0.25 |
| Creatinine (mg dL-1) | 1.59±0.62 | 1.51–1.69 | 1.75±0.71 | 1.28–2.22 | 0.44 |
| eGFR | 47.83±15.12 | 45.56–50.09 | 45.91±17.03 | 34.46–57.35 | 0.68 |
| Uric acid (mg dL-1) | 6.97±1.48 | 6.75–7.19 | 6.85±1.46 | 5.87–7.84 | 0.79 |
| Sodium (mmol L-1) | 141.21±3.57 | 140.67–141.75 | 139.45±3.11 | 137.37–141.54 | 0.11 |
| Potassium (mmol L-1) | 4.18±0.44 | 4.11–4.25 | 4.04±0.41 | 3.76–4.32 | 0.31 |

ALT – alanine transaminase; AST – aspartate transaminase; eGFR – estimated glomerular filtration rate.

It is postulated that C/D ratio remains the best way to assess treatment efficacy [15].

Analysing the correlations between the C/D ratio and parameters describing graft function, García-Sáiz et al. reported that it can be used for cyclosporine dosage adjustment after transplantation [16]. Our study showed that there is no correlation between the analysed polymorphisms and drug C/D ratio.

A study by Loh et al. also revealed that gene polymorphisms can influence dose requirements, but only in case of treatment based on tacrolimus [17]. It is suggested that the CYP3A4*1B polymorphism may be associated with enhanced CYP3A4 activity and can lead to the rapid metabolism of TAC [18]. However, the influence of CYP3A4*1B polymorphism on the TAC and CsA

pharmacokinetics in renal transplant patients is controversial because some authors showed that the CYP3A4*1B polymorphism may be associated with reduced enzymatic activity [8,19,20]. They suggest that the CYP3A4*1B polymorphism in the promoter of this gene has a stronger influence on protein expression than catalytic activity [21,22]. Furthermore, the effect of this polymorphism on enzymatic function is not the same for all drugs that are substrates for the CYP3A4 enzyme [22]. Several factors can influence the pharmacokinetics of CsA, including hepatic dysfunction, post-transplantation time, serum albumin, age, race, and drug interactions, especially gene polymorphism. In our study, patients were treated with CsA in a combination of MMF or Aza and corticosteroids, which may also influence the regimen of calcineurin inhibitors (these interactions were not included in our analysis). One must also consider the medicines

**Table 3.** Comparison of selected clinical and biochemical parameters between the genotypes of the 3435C>T (rs1045642) polymorphism of the MDR1 gene in patients receiving cyclosporine (CsA). Values normally distributed are expressed as means ± standard deviation (SD).

| Study group | CC n=45 | 95% CI | CT n=85 | 95% CI | TT n=54 | 95% CI | P |
|---|---|---|---|---|---|---|---|
| CsA dose (mg day-1) | 163.78± 44.85 | 150.29–177.26 | 172.06± 63.55 | 158.35–185.76 | 173.61± 68.23 | 154.98–192.23 | 0.69 |
| Concentration of CsA in the blood (ng ml-1) | 111.94± 49.91 | 96.95–126.94 | 115.22± 51.41 | 104.14–126.31 | 116.79± 42.77 | 105.11–128.46 | 0.88 |
| Weight (kg) | 81.47± 15.75 | 76.74–86.19 | 74.54± 17.82 | 70.67–78.41 | 83.79± 15.88 | 79.46–88.13 | 0.52 |
| BMI (kg m$^2$-1) | 27.64± 4.42 | 26.31–28.97 | 26.08± 5.16 | 24.97–27.19 | 28.89± 5.18 | 27.48–30.31 | 0.06 |
| Systolic blood pressure (mmHg) | 130.11± 11.55 | 126.64–133.58 | 132.94± 13.81 | 129.96–135.92 | 134.44± 13.27 | 130.82–138.07 | 0.07 |
| Diastolic blood pressure (mmHg) | 81.33± 9.79 | 78.39–84.27 | 83.12± 8.05 | 81.38–84.85 | 83.61± 7.42 | 81.58–85.63 | 0.36 |
| ALT (U L-1) | 19.73± 12.39 | 16.01–23.45 | 17.76± 8.97 | 15.83–19.69 | 21.26± 12.46 | 17.85–24.66 | 0.18 |
| AST (U L-1) | 20.36± 7.47 | 18.11–22.61 | 20.31± 9.09 | 18.34–22.27 | 21.39± 9.38 | 18.83–23.95 | 0.75 |
| Bilirubin (mg dL-1) | 0.61± 0.29 | 0.52–0.69 | 0.58± 0.29 | 0.52–0.65 | 0.62± 0.26 | 0.55–0.71 | 0.72 |
| Total cholesterol (mg dL-1) | 188.71± 35.94 | 177.78–199.63 | 188.35± 40.03 | 179.56–197.15 | 188.08± 42.11 | 176.23–199.92 | 0.99 |
| Cholesterol-HDL (mg dL-1) | 61.25± 21.91 | 53.61–68.91 | 61.66± 19.74 | 56.38–66.94 | 67.27± 20.69 | 59.81–74.72 | 0.39 |
| Cholesterol-LDL (mg dL-1) | 100.79± 33.81 | 88.99–112.59 | 94.35± 35.24 | 84.92–103.79 | 93.48± 40.29 | 78.71–108.26 | 0.65 |
| Triglycerides (mg dL-1) | 136.24± 55.91 | 116.72–155.74 | 139.59± 58.71 | 123.86–155.31 | 153.94± 83.48 | 123.83–184.04 | 0.49 |
| Total lipids (mg dL-1) | 637.15± 110.81 | 598.48–675.81 | 628.41± 123.39 | 595.37–661.46 | 660.84± 168.17 | 600.21–721.47 | 0.54 |
| Creatinine (mg dL-1) | 1.67± 0.72 | 1.45–1.89 | 1.63± 0.64 | 1.49–1.77 | 1.51± 0.51 | 1.37–1.65 | 0.40 |
| eGFR | 46.64± 15.63 | 41.94–51.33 | 47.07± 16.07 | 43.61–50.54 | 49.62± 13.41 | 45.96–53.28 | 0.54 |
| Uric acid (mg dL-1) | 7.03± 1.58 | 6.55–7.51 | 6.89± 1.53 | 6.56–7.22 | 7.03± 1.33 | 6.66–7.40 | 0.82 |
| Sodium (mmol L-1) | 141.91± 2.07 | 141.28–142.53 | 140.83± 3.44 | 140.08–141.58 | 140.85± 4.55 | 139.60–142.11 | 0.21 |
| Potassium (mmol L-1) | 4.17± 0.46 | 4.03–4.31 | 4.22± 0.44 | 4.13–4.32 | 4.09± 0.42 | 3.98–4.21 | 0.26 |

ALT – alanine transaminase; AST – aspartate transaminase; eGFR – estimated glomerular filtration rate.

used by patients without informing the attending physician. Gierek et al. showed that 63% of kidney transplant recipients are taking NSAIDs, with no awareness of possible consequences [23]. Taking into account factors such as age, body weight, BMI, and functional parameters of the kidneys and liver, we can conclude that these values did not affect the dosage of CsA. In addition, it has been shown that changes in some parameters are independent on the type of immunosuppressant used [24].

**Table 4.** The concentration of the CsA in the blood to the dose of the drug (C/D ratio) depending on genotype for polymorphisms of CYP3A4*1/*1B and MDR 3435C>T.

|  | Mean±SD | SEM | 95% CI | Min. | Max. | *P* |
|---|---|---|---|---|---|---|
| CYP3A4*1/*1B |  |  |  |  |  |  |
| *1/*1 | 0.707±0.289 | 0.022 | 0.664–0.751 | 0.01 | 1.75 | 0.986 |
| *1/*1B | 0.711±0.278 | 0.084 | 0.524–0.897 | 0.35 | 1.26 | |
| Total | 0.707±0.287 | 0.021 | 0.665–0.749 | 0.01 | 1.75 | |
| MDR1 3435C>T |  |  |  |  |  |  |
| CC | 0.708±0.311 | 0.046 | 0.615–0.802 | 0.01 | 1.57 | 0.997 |
| CT | 0.705±0.304 | 0.033 | 0.639–0.771 | 0.02 | 1.75 | |
| TT | 0.709±0.241 | 0.033 | 0.643–0.775 | 0.35 | 1.39 | |
| Total | 0.707±0.287 | 0.021 | 0.665–0.749 | 0.01 | 1.75 | |

We also examined the influence of 3435C>T MDR1 polymorphism on the dose and blood concentration of immunosuppressive drugs. Our analysis demonstrated that patients with the CC genotype for MDR1 3435C>T polymorphism received lower doses of CsA than carriers with the CT and TT genotypes. Regarding the average drug concentration in the blood, we did not observe differences between the distribution of genotypes for MDR1 3435C>T polymorphism. Again, the analysis of correlations with C/D ratio showed no significant differences.

von Ahsen et al. found no effect of the MDR1 3435C>T polymorphism on dose-adjusted CsA trough concentrations or rejection incidence in stable renal transplant recipients, suggesting that MDR1 3435C>T polymorphism is not the major determinant of CsA efficacy in renal transplant patients [25]. In addition, a meta-analysis conducted among renal transplant recipients showed that 3435CC carriers require a higher dose of CsA to achieve target therapeutic concentrations compared to 3435TT carriers, especially in the Asian population, and especially during the early and middle time periods after renal transplantation [26].

Another study found no significant correlation between CsA trough concentrations or dose requirements with the MDR1 and the CYP3A5*1 genotypes [27]. Similar results were obtained by Ashavaid et al., who concluded that MDR1 polymorphism does not influence CsA dose requirements, but it may be useful in therapy based on tacrolimus [28]. A meta-analysis performed by Jiang et al. found no correlation between the SNP 3435C>T in the MDR1 and pharmacokinetics of CsA, but suggest that ethnic differences are possible [29].

## Conclusions

The characterization of CYP3A4*1B and MDR1 polymorphisms cannot provide useful guidance for individualizing CsA dosages in renal transplant patients by indicating the optimal dose of these drugs without exposing patients to possible adverse effects, associated mainly with nephrotoxicity. Furthermore, the few studies that have focused on the interaction between MDR1 and CYP3A4 polymorphisms on CsA in renal transplant patients provided insufficient data. A combination of CYP3A4/5 and MDR1 genotypes might a better predictor than any single gene. Hence, further studies on the gene-gene interactions that affect drug pharmacokinetics may be helpful to understand the complex mechanism of the above interaction, and to translate this knowledge to determining individual patient needs for immunosuppressive therapy.

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