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Race, Calcineurin Inhibitor Exposure, and Renal Function After Solid Organ Transplantation

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ABSTRACT

Background. Calcineurin-inhibitor (CNI)–induced nephrotoxicity frequently complicates transplantation. African-Americans are at a greater risk of renal failure than the general population. We investigated whether race was an effect modifier of the relationship between CNI exposure and kidney function after nonrenal solid organ transplantation.

Methods. This is a retrospective cohort study of 1609 patients who underwent initial nonrenal solid organ transplantation between January 2000 and June 2012. A central repository administrative database was queried electronically for demographics, comorbidities, and serial levels of tacrolimus, cyclosporine, and serum creatinine. Predictors of interest were total drug exposure of tacrolimus and cyclosporine (area under the concentration–time curve) and self-reported race. The outcome of interest was cumulative change in estimated glomerular filtration rate (GFR).

Results. There were 1109 patients treated with tacrolimus (271 African-Americans) and 500 patients treated with cyclosporine (113 African Americans). A decline in GFR over time was seen with total tacrolimus exposure (−1.3 mL/min/1.73 m^2 for every 5 ng/mL·year increase in tacrolimus) and total cyclosporine exposure (−1.1 mL/min/1.73 m^2 for every 50 ng/mL·year increase in cyclosporine). However, total CNI exposure effect on estimated GFR changes did not vary by race (*P* interaction was 0.9 for tacrolimus and 0.6 for cyclosporine).

Conclusions. Total CNI exposure is associated with worsening kidney function among patients with nonrenal solid organ transplantation. However, African-American patients are not more vulnerable to chronic CNI-induced nephrotoxicity when compared to white patients.

CALCINEURIN INHIBITORS (CNIs) such as cyclosporine and tacrolimus have made possible the modern era of transplantation medicine, resulting in substantial improvement in success rates after solid organ transplantation [1–3]. Unfortunately, these medications, which are the cornerstone of post-transplantation immunosuppressive therapy, carry with them a number of adverse side effects [4]. The nephrotoxic effects of cyclosporine and tacrolimus are a major concern in solid organ transplantation and many other diseases that require therapy with these drugs [2,5–7]. Calcineurin inhibitor exposure is associated with irreversible changes in blood vessels (arterial hyalinosis), tubulointerstitium (tubular atrophy and interstitial fibrosis), and glomeruli (thickening and fibrosis of Bowman's capsule and focal segmental or global glomerular sclerosis) [8–10]. Progressive renal dysfunction plagues recipients of solid organ transplants with a 5-year risk of chronic renal failure (defined as glomerular filtration rate [GFR] <30 mL/min/1.73 m^2) that ranges from 7% to 21%, depending on the type of organ transplanted [6].

Post-transplantation graft and patient outcomes have previously been shown to vary by recipient race [11–15], which is thought to be due to a variety of issues ranging from immune reactivity to access to medical care [16–18]. Moreover, African-Americans are known to disproportionately suffer from kidney disease, possibly due to high rates

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of coexisting hypertension and diabetes and access to health care [19]. Despite this, whether there is racial disparity in terms of the nephrotoxic effects of CNIs is not clear. The very few studies that reported on racial differences in chronic CNI-induced nephrotoxicity rates had several limitations, namely small number of patients, short period of follow-up, and failure to account for degree of exposure. With these considerations in mind, we conducted a large retrospective study of patients with nonrenal solid organ transplants to investigate whether the correlation of CNI exposure (measured as area under the time–concentration curve) and renal function differed by self-identified race.

MATERIAL AND METHODS

Study Population and Participants

We conducted a retrospective cohort study utilizing an administrative-linked electronic database of patients in the Henry Ford Health System in Michigan. The system includes several hospitals, a multispecialty physician group of approximately 1000 physicians, and an affiliated health maintenance organization. The system maintains a central repository of administrative data that we queried for this study. Using electronic data sources, we identified 1609 patients 18 years of age or older who underwent initial solid organ transplantation (cardiac, lung, or liver) between January 2000 and June 2012, and who survived the hospitalization and were discharged. A master patient index contained demographic data (i.e. date of birth, sex, and race). All subject-specific variables and laboratory measurements were obtained from electronic medical records. Patients who underwent renal transplantation were excluded because the impact of CNI exposure on a transplanted kidney may differ from that of a native kidney. Creatinine level at discharge from transplantation hospitalization was considered baseline. The observation period for each individual lasted from discharge until the time of death, loss to follow-up, or onset of dialysis. The study was approved by the Henry Ford Hospital Institutional Review Board.

Outcome of Interest

The outcome of interest was the cumulative change in estimated GFR (eGFR). Cumulative change in eGFR for each individual was defined as the sum of the differences between any observed eGFR and baseline eGFR. The 4-variable Modification of Diet in Renal Disease study equation was used to calculate eGFR.

Primary Predictors

The predictors of interest were total tacrolimus exposure, total cyclosporine exposure (area under concentration-time curve), and self-reported race. Total CNI exposure was defined as the sum of areas under the curves between 2 consecutive CNI levels over time.

Covariates of Interest

Covariates of interest were age, sex, eGFR on day of discharge from the hospital post-transplantation, diabetes, and hypertension. Age reflected the measurement at the date of transplantation. Sex was determined by self-report. Hypertension and diabetes were determined through electronic medical records based on *International Classification of Diseases, Ninth Revision* (ICD-9) codes.

Statistical Analysis

We used generalized estimating equations to test the association between total cumulative tacrolimus or cyclosporine exposure over time and cumulative changes in eGFR from baseline, including adjustment for age, gender, hypertension, diabetes, and baseline kidney function. The data from each individual consisted of changes in cumulative changes in eGFR from any measure to baseline and an area under the curve, from measure to measure, for the drug in question. To relate the two, a linear regression model was implemented using a generalized estimating equation approach. This approach was used to model the correlation within the cluster of values for an individual. χ^2 tests for categorical variables and Student t test for continuous variables were used to compare the groups in Table 1. P values $<.05$ were considered positive for main effects. $P < .1$ was considered positive for interaction of either CNI with race. All analyses were performed using SAS 9.4 (SAS Institute Inc., Cary, N.C., United States).

RESULTS

Of the 1609 patients identified, 1109 patients were treated with tacrolimus (271 African-Americans) and 500 were treated with cyclosporine (113 African-Americans) (Fig 1). Demographics and baseline characteristics stratified by race are shown in Table 1. History of hypertension was more prevalent in African-Americans than whites. African-Americans were younger, had a higher proportion of females, and slightly higher eGFRs than whites. Multivariate modeling adjusted for age, gender, hypertension, diabetes, and baseline kidney function showed that total tacrolimus and cyclosporine exposure over time were associated with eGFR decline ($P < .001$) but this effect did not vary by race for either drug ($P_{interaction} = .9$ for cross-product term of total tacrolimus exposure and race; $P_{interaction} = .6$ for cross product term of total cyclosporine exposure and race). Tables 2 and 3 show the multivariate models for the association between cumulative changes in eGFR and total exposure to tacrolimus/cyclosporine. For each 5 ng/mL·years of tacrolimus exposure, the eGFR decreased by approximately 1.3 mL/min/1.73 m^2. For each 50 ng/mL·years of cyclosporine exposure, the eGFR decreased by approximately 1.1 mL/min/1.73 m^2.

DISCUSSION

The introduction of CNIs has revolutionized transplantation medicine. They are now widely used as immunosuppressant

Table 1. Clinical Characteristics Stratified by Race

	Whites n = 1225	African Americans n = 384	*P* Value
Hypertension, n (%)	81 (6.6)	43 (11.2)	.003
Diabetes, n (%)	273 (22.3)	89 (23.2)	.715
Female, n (%)	427 (34.9)	164 (42.7)	.005
Age (y), mean ± SD	54.4 ± 10	49.9 ± 11.6	.001
Baseline GFR (mL/min/1.73 m^2), mean ± SD	82.9 ± 42.6	93.9 ± 59.8	.001
Creatinine (mg/dL), mean ± SD	1.20 ± 0.91	1.22 ± 0.67	.003

Conversion factors for units: serum creatinine in mg/dL to μmol/L, ×88.4.
Abbreviations: GFR, glomerular filtration rate; SD, standard deviation.

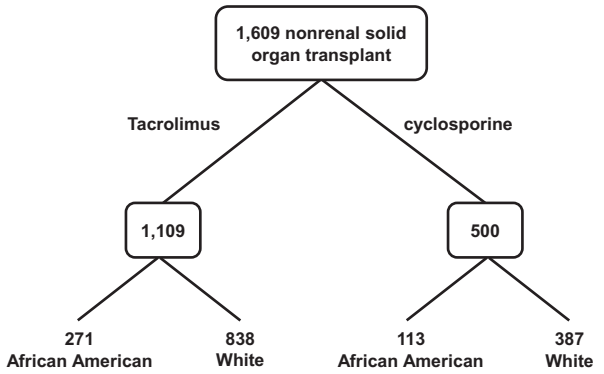

Fig 1. Number of patients exposed to either cyclosporine or tacrolimus by self-identified race.

therapy for liver, renal, cardiac, and lung transplantation. Patients treated with the CNIs cyclosporine and tacrolimus are at a high risk of developing renal injury [20]. Nephrotoxicity can be divided into acute and chronic forms. Acute nephrotoxicity is primarily associated with profound alterations in vascular flow [21–23] and vasoconstriction of preglomerular afferent arterioles [24] and is largely reversible after reducing the dose. Other forms of acute nephrotoxicity include tubular dysfunction and rarely thrombotic microangiopathy/hemolytic uremic syndrome [25–27]. Chronic CNI-induced nephrotoxicity, which is usually irreversible, results from arteriolar hyalinosis, tubular atrophy, interstitial fibrosis, and glomerular sclerosis [28–31]. It remains quite difficult to recognize patients who are most likely to develop chronic CNI-induced kidney nephrotoxicity.

African American patients have an unequal share of renal disease. Suggested explanations for this racial disparity include a higher prevalence of diabetes mellitus and hypertension among African Americans [32–35], increased inherited predisposition of African Americans to kidney damage [36,37], and lower socioeconomic status among African Americans [38–40]. Racial differences with regards to the effects of CNI-induced nephrotoxicity have not been investigated in detail. We performed a literature search and found no large cohort studies that reported on racial differences in the renal toxic effects of CNIs.

Table 2. Multivariate Model Showing Association of Cumulative eGFR Change and Total Tacrolimus Exposure After Adjusting for Race, Gender, Age, Hypertension, Diabetes, and Baseline Glomerular Filtration Rate

Variable	Cumulative eGFR Change (mL/min/1.73 m^2) Estimate ± SD	*P* Value
Tacrolimus exposure (per 5 ng/mL·year increase)	−1.30 ± 0.22	.001
African Americans	4.95 ± 2.50	.048
Female	5.00 ± 1.97	.010
Age (per 10-year increase)	4.05 ± 1.08	.001
Hypertension	11.2 ± 2.28	.001
Diabetes	4.12 ± 1.76	.019
Baseline eGFR (mL/min/1.73 m^2)	0.45 ± 0.05	.001

Abbreviations: eGFR, estimated glomerular filtration rate; SD, standard deviation.

Table 3. Multivariate Model Showing Association of Cumulative eGFR Change and Total Cyclosporine Exposure After Adjusting for Race, Gender, Age, Hypertension, Diabetes, and Baseline Glomerular Filtration Rate

Variable	Cumulative eGFR Change (mL/min/1.73 m^2) Estimate ± SD	*P* value
Cyclosporine exposure (per 50 ng/mL·year increase)	−1.13 ± 0.15	.001
African Americans	3.88 ± 3.02	.199
Female	−8.57 ± 2.47	.001
Age (per 10-year increase)	−7.34 ± 1.38	.001
Hypertension	−6.42 ± 2.61	.014
Diabetes	0.61 ± 2.40	.798
Baseline eGFR (mL/min/1.73 m^2)	−0.61 ± 0.03	.001

Abbreviations: eGFR, estimated glomerular filtration rate; SD, standard deviation.

The 3 studies that we came across all had small patient numbers and short analytical horizons, and none were primarily designed to evaluate ethnic variation in kidney dysfunction. Two of these studies were in kidney transplant patients in whom, in addition to CNI-induced nephrotoxicity, a variety of other causes could have contributed to progressive kidney dysfunction, such as recurrence of primary kidney disease and acute or chronic rejection. In 1 multicenter randomized clinical trial of 205 (25% African Americans) designed primarily to compare patient survival and renal graft survival between recipients of cyclosporine and tacrolimus, the serum creatinine levels were similar across race and treatment groups through 1 year after transplantation [41]. In another prospective study of 63 heart transplant patients (63% African Americans) designed primarily to compare acute rejection, patient survival, and renal graft survival of tacrolimus and mycophenolate regimens, no differences in renal function were noted at 1 year in the tacrolimus-treated African American or white groups [42]. Finally, a retrospective study of 114 patients (24% African American) evaluated acute rejection rates of kidney transplant between African American and white patients receiving a combination of tacrolimus, sirolimus, and corticosteroids. Although the long-term survival rates were low in the African American patients when compared to the white patients, there was no significant difference in the renal toxicity effects in both races [43].

From the review of these studies, we found that there has been no extensive study in a large patient population to determine the racial differences in terms of the exposure to tacrolimus and cyclosporine. We studied 1609 nonrenal solid organ transplant patients and the results showed that total CNI exposure was associated with worsening kidney function. However, these patients were not more susceptible to the effects of CNIs when compared to whites. In contrast to other studies in which kidney function at specific time

points between 2 races were compared without adjustment for total drug exposure, we studied the effects of total CNI exposure on kidney function, measured as area under the concentration-time curve. We chose total area under the curve as opposed to total amount of CNI administered as a surrogate of total exposure because of unpredictable dose–concentration relationship with CNIs [44,45] and variability in absorption, metabolism, and elimination of these compounds [46–51].

Our study has several limitations. The observational nature of our investigation renders the study subject selection to bias and confounding. We tried to limit selection bias by including all patients between the specified dates with no restriction for inclusion. Potential for confounding was addressed by adjusting for several factors known to affect renal function, specifically age, blood pressure, and diabetes status. In addition, we excluded kidney transplant patients considering that the impact of CNI exposure on a transplanted kidney may differ from that of a native kidney. Moreover, African American kidney transplant patients have higher rates of acute kidney rejection and this may potentially confound the association of CNIs on eGFR and the relationship to race (i.e. changes in eGFR could be due to CNI or rejection). Our study was based on electronic administrative data, and thus information on comorbidities is dependent on accurate coding; however, this would not be expected to yield a systematic error that would affect our analysis and this approach brings the advantage of adequate sample size. We did not examine episodes of acute kidney injury, which likely feature a different pathophysiology, so this cannot be commented upon within the current work. Finally, because no routine kidney biopsies are performed in nonrenal transplant recipients, no data are available on histologic changes to support a definite diagnosis of CNI nephrotoxicity.

In conclusion, cumulative CNI exposure was associated with GFR decline; however, this did not differ by self-identified race. Specifically, African American patients do not appear to be more vulnerable to CNI-induced chronic renal dysfunction when compared to white patients.

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REFERENCES

[1] van Sandwijk MS, Bemelman FJ, Ten Berge IJ. Immunosuppressive drugs after solid organ transplantation. Neth J Med 2013;71:281–9.

[2] Olyaei AJ, de Mattos AM, Bennett WM. Nephrotoxicity of immunosuppressive drugs: new insight and preventive strategies. Curr Opin Crit Care 2001;7:384–9.

[3] Merville P. Combating chronic renal allograft dysfunction: optimal immunosuppressive regimens. Drugs 2005;65:615–31.

[4] Marcen R. Immunosuppressive drugs in kidney transplantation: impact on patient survival, and incidence of cardiovascular disease, malignancy and infection. Drugs 2009;69:2227–43.

[5] Myers BD, Ross J, Newton L, Luetscher J, Perlroth M. Cyclosporine-associated chronic nephropathy. N Engl J Med 1984;311:699–705.

[6] Ojo AO, Held PJ, Port FK, Wolfe RA, Leichtman AB, Young EW, et al. Chronic renal failure after transplantation of a nonrenal organ. N Engl J Med 2003;349:931–40.

[7] Palestine AG, Austin 3rd HA, Balow JE, Antonovych TT, Sabnis SG, Preuss HG, et al. Renal histopathologic alterations in patients treated with cyclosporine for uveitis. N Engl J Med 1986;314:1293–8.

[8] Mihatsch MJ, Kyo M, Morozumi K, Yamaguchi Y, Nickeleit V, Ryffel B. The side-effects of ciclosporine-A and tacrolimus. Clin Nephrol 1998;49:356–63.

[9] Morozumi K, Takeda A, Uchida K, Mihatsch MJ. Cyclosporine nephrotoxicity: how does it affect renal allograft function and transplant morphology? Transplant Proc 2004;36:251S–6S.

[10] Randhawa PS, Shapiro R, Jordan ML, Starzl TE, Demetris AJ. The histopathological changes associated with allograft rejection and drug toxicity in renal transplant recipients maintained on FK506. Clinical significance and comparison with cyclosporine. Am J Surg Pathol 1993;17:60–8.

[11] Cohen O, De La Zerda D, Beygui RE, Hekmat D, Laks H. Ethnicity as a predictor of graft longevity and recipient mortality in heart transplantation. Transplant Proc 2007;39:3297–302.

[12] Nair S, Eustace J, Thuluvath PJ. Effect of race on outcome of orthotopic liver transplantation: a cohort study. Lancet 2002;359:287–93.

[13] Neff GW, Kemmer N, Kaiser T, Zacharias V, Majoras N, Safdar K. Outcomes in adult and pediatric liver transplantation among various ethnic groups. Transplant Proc 2007;39:3204–6.

[14] Opelz G, Pfarr E, Engelmann A, Keppel E. Kidney graft survival rates in black cyclosporine-treated recipients. Collaborative Transplant Study. Transplant Proc 1989;21:3918–20.

[15] Butkus DE, Meydrech EF, Raju SS. Racial differences in the survival of cadaveric renal allografts. Overriding effects of HLA matching and socioeconomic factors. N Engl J Med 1992;327:840–5.

[16] Yoo HY, Thuluvath PJ. Outcome of liver transplantation in adult recipients: influence of neighborhood income, education, and insurance. Liver Transpl 2004;10:235–43.

[17] Pamboukian SV, Costanzo MR, Meyer P, Bartlett L, McLeod M, Heroux A. Influence of race in heart failure and cardiac transplantation: mortality differences are eliminated by specialized, comprehensive care. J Card Fail 2003;9:80–6.

[18] Lederer DJ, Caplan-Shaw CE, O'Shea MK, Wilt JS, Basner RC, Bartels MN, et al. Racial and ethnic disparities in survival in lung transplant candidates with idiopathic pulmonary fibrosis. Am J Transplant 2006;6:398–403.

[19] Tarver-Carr ME, Powe NR, Eberhardt MS, LaVeist TA, Kington RS, Coresh J, et al. Excess risk of chronic kidney disease among African American versus white subjects in the United States: a population-based study of potential explanatory factors. J Am Soc Nephrol 2002;13:2363–70.

[20] Burdmann EA, Andoh TF, Yu L, Bennett WM. Cyclosporine nephrotoxicity. Semin Nephrol 2003;23:465–76.

[21] Barros EJ, Boim MA, Ajzen H, Ramos OL, Schor N. Glomerular hemodynamics and hormonal participation on cyclosporine nephrotoxicity. Kidney Int 1987;32:19–25.

[22] Laskow DA, Curtis J, Luke R, Jones P, Barber H, Deierhoi M, et al. Cyclosporine impairs the renal response to volume depletion. Transplant Proc 1988;20:568–71.

[23] Laskow DA, Curtis JJ, Luke RG, Julian BA, Jones P, Deierhoi MH, et al. Cyclosporine-induced changes in glomerular filtration rate and urea excretion. Am J Med 1990;88:497–502.

[24] English J, Evan A, Houghton DC, Bennett WM. Cyclosporine-induced acute renal dysfunction in the rat. Evidence of arteriolar vasoconstriction with preservation of tubular function. Transplantation 1987;44:135–41.

[25] Franz M, Regele H, Schmaldienst S, Stummvoll HK, Horl WH, Pohanka E. Posttransplant hemolytic uremic syndrome

in adult retransplanted kidney graft recipients: advantage of FK506 therapy? Transplantation 1998;66:1258–62.

[26] Yango A, Morrissey P, Monaco A, Butera J, Gohh RY. Successful treatment of tacrolimus-associated thrombotic microangiopathy with sirolimus conversion and plasma exchange. Clin Nephrol 2002;58:77–8.

[27] Lin CC, King KL, Chao YW, Yang AH, Chang CF, Yang WC. Tacrolimus-associated hemolytic uremic syndrome: a case analysis. J Nephrol 2003;16:580–5.

[28] de Mattos AM, Olyaei AJ, Bennett WM. Nephrotoxicity of immunosuppressive drugs: long-term consequences and challenges for the future. Am J Kidney Dis 2000;35:333–46.

[29] Kahan BD. Cyclosporine. N Engl J Med 1989;321:1725–38.

[30] Kopp JB, Klotman PE. Cellular and molecular mechanisms of cyclosporin nephrotoxicity. J Am Soc Nephrol 1990;1:162–79.

[31] Naesens M, Kuypers DR, Sarwal M. Calcineurin inhibitor nephrotoxicity. Clin J Am Soc Nephrol 2009;4:481–508.

[32] McClellan W, Tuttle E, Issa A. Racial differences in the incidence of hypertensive end-stage renal disease (ESRD) are not entirely explained by differences in the prevalence of hypertension. Am J Kidney Dis 1988;12:285–90.

[33] Whittle JC, Whelton PK, Seidler AJ, Klag MJ. Does racial variation in risk factors explain black-white differences in the incidence of hypertensive end-stage renal disease? Arch Intern Med 1991;151:1359–64.

[34] Cowie CC, Port FK, Wolfe RA, Savage PJ, Moll PP, Hawthorne VM. Disparities in incidence of diabetic end-stage renal disease according to race and type of diabetes. N Engl J Med 1989;321:1074–9.

[35] Stephens GW, Gillaspy JA, Clyne D, Mejia A, Pollak VE. Racial differences in the incidence of end-stage renal disease in types I and II diabetes mellitus. Am J Kidney Dis 1990;15:562–7.

[36] Freedman BI. Renal microvascular susceptibility in African American pedigrees. Transplant Proc 1993;25:2423–5.

[37] Freedman BI, Espeland MA, Heise ER, Adams PL, Buckalew Jr VM, Canzanello VJ. Racial differences in HLA antigen frequency and hypertensive renal failure. Am J Hypertens 1991;4:393–8.

[38] Byrne C, Nedelman J, Luke RG. Race, socioeconomic status, and the development of end-stage renal disease. Am J Kidney Dis 1994;23:16–22.

[39] Perneger TV, Whelton PK, Klag MJ. Race and end-stage renal disease. Socioeconomic status and access to health care as mediating factors. Arch Intern Med 1995;155:1201–8.

[40] Young EW, Mauger EA, Jiang KH, Port FK, Wolfe RA. Socioeconomic status and end-stage renal disease in the United States. Kidney Int 1994;45:907–11.

[41] Neylan JF. Racial differences in renal transplantation after immunosuppression with tacrolimus versus cyclosporine. FK506 Kidney Transplant Study Group. Transplantation 1998;65:515–23.

[42] Mehra MR, Uber PA, Scott RL, Park MH. Ethnic disparity in clinical outcome after heart transplantation is abrogated using tacrolimus and mycophenolate mofetil-based immunosuppression. Transplantation 2002;74:1568–73.

[43] El-Sabrout R, Delaney V, Butt F, Qadir M, Hanson P, Tuteja S, et al. African American and Caucasian renal transplant recipients have equal acute rejection rates under sirolimus and tacrolimus combination therapy. Graft 2002;5:455–61.

[44] Fahr A. Cyclosporin clinical pharmacokinetics. Clin Pharmacokinet 1993;24:472–95.

[45] Staatz CE, Tett SE. Clinical pharmacokinetics and pharmacodynamics of tacrolimus in solid organ transplantation. Clin Pharmacokinet 2004;43:623–53.

[46] Maes BD, Lemahieu W, Kuypers D, Evenepoel P, Coosemans W, Pirenne J, et al. Differential effect of diarrhea on FK506 versus cyclosporine A trough levels and resultant prevention of allograft rejection in renal transplant recipients. Am J Transplant 2002;2:989–92.

[47] Lemahieu W, Maes B, Verbeke K, Rutgeerts P, Geboes K, Vanrenterghem Y. Cytochrome P450 3A4 and P-glycoprotein activity and assimilation of tacrolimus in transplant patients with persistent diarrhea. Am J Transplant 2005;5:1383–91.

[48] Hesselink DA, van Gelder T, van Schaik RH, Balk AH, van der Heiden IP, van Dam T, et al. Population pharmacokinetics of cyclosporine in kidney and heart transplant recipients and the influence of ethnicity and genetic polymorphisms in the MDR-1, CYP3A4, and CYP3A5 genes. Clin Pharmacol Ther 2004;76:545–56.

[49] Anglicheau D, Verstuyft C, Laurent-Puig P, Becquemont L, Schlageter MH, Cassinat B, et al. Association of the multidrug resistance-1 gene single-nucleotide polymorphisms with the tacrolimus dose requirements in renal transplant recipients. J Am Soc Nephrol 2003;14:1889–96.

[50] 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;74:245–54.

[51] Macphee IA, Fredericks S, Tai T, Syrris P, Carter ND, Johnston A, et al. Tacrolimus pharmacogenetics: polymorphisms associated with expression of cytochrome p4503A5 and P-glycoprotein correlate with dose requirement. Transplantation 2002;74:1486–9.