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Race, calcineurin inhibitor exposure and renal function after solid organ transplantation

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Abstract

Background—Calcineurin inhibitor 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 calcineurin inhibitor exposure and kidney function after nonrenal solid organ transplant.

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.

Results—There were 1109 patients treated with tacrolimus (271 African Americans) and 500 patients treated with cyclosporine (113 African Americans). A decline in glomerular filtration rate over time was seen with total tacrolimus exposure (-1.3 ml/min/1.73 m² for every 5 ng/ml.year increase in tacrolimus) and total cyclosporine exposure (-1.1 ml/min/1.73 m² for every 50 ng/ml.year increase in cyclosporine). However, total calcineurin inhibitor exposure effect on

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estimated glomerular filtration rate changes did not vary by race (P interaction was 0.9 for tacrolimus and 0.6 for cyclosporine).

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

Keywords

calcineurin inhibitors; creatinine; cyclosporine; glomerular filtration rate; race; renal function; tacrolimus

INTRODUCTION

Calcineurin inhibitors like 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-transplant 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), tubulo-interstitium (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 five-year risk of chronic renal failure (defined as glomerular filtration rate < 30ml/min/1.73 m²) that ranges from 7% to 21%, depending on the type of organ transplanted [6].

Post-transplantation graft and patient outcomes have been previously 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 of coexisting hypertension, diabetes and access to healthcare [19]. Despite this, whether there is racial disparity in terms of the nephrotoxic effects of calcineurin inhibitors is not clear. The very few studies that reported on racial differences in chronic calcineurin inhibitor (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 to investigate whether the correlation of calcineurin inhibitor 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, which 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. 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 glomerular filtration rate (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 calcineurin inhibitor 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 transplant. Sex was determined by self-report. Hypertension and diabetes were determined through electronic medical records based on International Classification of Diseases, Ninth Revision, 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. Chi-squared tests for categorical variables and Student's t-test for continuous variables were used to compare the groups in Table 1. P values < 0.05 were considered positive for main effects. $P < 0.1$ was considered positive for interaction of either calcineurin inhibitor with race. All analyses were performed using SAS 9.4 (SAS Institute, Inc., Cary, NC).

RESULTS

Of the 1609 patients identified, 1109 patients were treated with tacrolimus (271 African Americans) and 500 were treated with cyclosporine (113 African Americans) (Figure 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 ($P < 0.001$) but this effect did not vary by race for either drug ($P_{interaction} = 0.9$ for cross product term of total tacrolimus exposure and race; $P_{interaction} = 0.6$ 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 ~ 1.3 ml/min/1.73 m². For each (50 ng/ml).years of cyclosporine exposure, the eGFR decreased by ~ 1.1 ml/min/1.73 m².

DISCUSSION

The introduction of CNIs has revolutionized transplantation medicine. They are now widely used as immunosuppressant therapy for liver, renal, cardiac and lung transplantation. Patients treated with the calcineurin inhibitors 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 pre-glomerular 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.

The 3 studies that we came across all had small patient numbers, short analytical horizons and none were primarily designed to evaluate ethnic variation in kidney dysfunction. Two of these studies were in kidney transplant patients where 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 one 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 transplant [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 at 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 the CNIs 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 where kidney function at specific time points between two 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 calcineurin inhibitor on eGFR and the relationship to race (i.e., changes in eGFR could be due to CIN 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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- Total calcineurin-inhibitor exposure is associated with eGFR decline;
- African American patients are not more vulnerable to chronic calcineurin-inhibitor induced nephrotoxicity when compared to white patients.

Figure 1. Study Scheme

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

Table 1

Clinical Characteristics Stratified by Race.

	Whites n=1225	African Americans n=384	P
Hypertension, n (%)	81 (6.6)	43 (11.2)	0.003
Diabetes, n (%)	273 (22.3)	89 (23.2)	0.715
Female, n (%)	427 (34.9)	164 (42.7)	0.005
Age (years), mean $\pm$ SD	54.4 $\pm$ 10	49.9 $\pm$ 11.6	0.001
Baseline GFR (ml/min/1.73m ²), mean $\pm$ SD	82.9 $\pm$ 42.6	93.9 $\pm$ 59.8	0.001
Creatinine (mg/dL), mean $\pm$ SD	1.20 $\pm$ 0.91	1.22 $\pm$ 0.67	0.003

Conversion factors for units: serum creatinine in mg/dL to μ mol/L, $\times 88.4$

Abbreviations: GFR, glomerular filtration rate; SD, standard deviation.

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.

Cumulative eGFR Change (ml/min/1.73 m ²)		
Variable	Estimate ± SD	P-value
Tacrolimus exposure (per 5 ng/ml.year increase)	-1.30 ± 0.22	0.001
African Americans	4.95 ± 2.50	0.048
Female	5.00 ± 1.97	0.010
Age (per 10 years increase)	4.05 ± 1.08	0.001
Hypertension	11.2 ± 2.28	0.001
Diabetes	4.12 ± 1.76	0.019
Baseline eGFR (ml/min/1.73 m ²)	0.45 ± 0.05	0.001

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.

Cumulative eGFR Change (ml/min/1.73 m ²)		
Variable	Estimate ± SD	P-value
Cyclosporine exposure (per 50 ng/ml.year increase)	-1.13 ± 0.15	0.001
African Americans	3.88 ± 3.02	0.199
Female	-8.57 ± 2.47	0.001
Age (per 10 year increase)	-7.34 ± 1.38	0.001
Hypertension	-6.42 ± 2.61	0.014
Diabetes	0.61 ± 2.40	0.798
Baseline eGFR (ml/min/1.73 m ²)	-0.61 ± 0.03	0.001

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