Optimal Blood Concentration of Cyclosporine Among Iranian Kidney Transplant Recipients

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Keywords. cyclosporine A, Kinetics, predictive value of tests, treatment outcome

Introduction. Clinical information concerning cyclosporine dose reduction in Iranian kidney transplant recipients is limited. There are data in Asian, Caucasian, and Iranian ethnic kidney transplant recipients that recommend the trough level (C0) and 2-hour postdose level (C2) of cyclosporine may be different. Our aim was to determine therapeutic levels of C0 and C2 at different time after transplantation among Iranian transplant patients.

Materials and Methods. Blood concentrations of cyclosporine were assessed in 4419 samples of kidney transplant recipients between 2008 and 2010. The patients were divided into 3 groups according to the time of laboratory studies (< 3 months, 4 to 12 months, and > 1 year after transplantation). Both univariable and multivariable analyses were performed to determine the correlation between cyclosporine blood levels and serum creatinine.

Results. A total of 1270 kidney transplant patients with 4419 blood samples enrolled. The mean age of the donor was 28 ± 6 years (range, 6 to 64 years) and 82.6% were men and 17.4% were women. In the subset of patients with serum creatinine values of at least 1.6 mg/dL for men and 1.4 mg/dL for women, we determined C0 and C2 levels between therapeutic and undertherapeutic creatinine ranges at 3 different time interval after transplantation, as follows: the first 3 months, 230 ng/mL to 240 ng/mL and 725 ng/mL to 775 ng/mL; 4 to 12 months, 135 ng/mL to 156 ng/mL and 535 ng/mL to 612 ng/mL; and after 1 year, 95 ng/mL to 120 ng/mL and 420 ng/mL to 479 ng/mL for C0 and C2, respectively.

Conclusions. The present study suggests that the cyclosporine levels for Iranian kidney transplant patients are lower compared to the recommended levels in western countries.

IJKD 2012;6:373-9
www.ijkd.org

Original Paper

INTRODUCTION

Calcineurin inhibitors, mainly cyclosporine A, have had an innovator effect on the overall success of kidney transplantation through a decrease in early immunologic injury and acute rejection rates. Cyclosporine is the major immunosuppressive agent currently used for kidney transplants[1]; however, its nephrotoxicity is one of the important causes of chronic kidney allograft dysfunction. The most advantageous protective dose of cyclosporine is an important concern because the sufficient blood level of cyclosporine required to prevent the allograft rejection is a narrow curative blood level in kidney transplant patients. In addition, the cost of drug and its nephrotoxicity are the two major restrictive factors related with chronic use of cyclosporine.[2] Nephrotoxicity allied with calcineurin inhibitors can cause kidney dysfunction, which is an independent risk factor for graft loss and mortality after kidney transplantation. Mortality of kidney

transplant recipients resulted from cardiovascular disease, infection, and malignancies are important reasons for cyclosporine dose reduction in kidney transplant recipients, since this medication can indirectly cause them.[3] Therefore, the investigation of the most beneficial immunosuppressive therapy continues to be crucial in kidney transplantation.[4]

The optimal cyclosporine exposure in kidney transplant recipients is difficult to achieve because of variability in cyclosporine pharmacokinetics. Knowing more about individual and ethnic difference in cyclosporine exposures can help us to provide more individualized therapy.[5] The dose with a most favorable risk-to-benefit proportion has not been recognized.[6] A nonquantitative summary of the current evidence suggests that calcineurin inhibitor minimization is safe and efficient after kidney transplantation. With enhanced short-term and medium-term consequences, this evidence becomes more important.[7] As a better kidney function is associated with better graft and patient survival, calcineurin inhibitor minimization protocols have been more developed. These protocols caused an improvement in kidney function in a large number of population transplanted according to several studies.[8,9] A great decrease in calcineurin inhibitor is allied with a better enhancement in kidney function.[10] Data relating to the impact of maintenance immunosuppression dose reductions posttransplant are currently limited; however, there is a study that shows that in kidney transplant recipients with good graft function, withdrawing maintenance cyclosporine, or reducing the dose of these drugs below certain thresholds after the first year posttransplant, is coupled with a significant increase in the risk of graft loss.[11]

Clinical information about the cyclosporine dose reduction in Iranian kidney transplant recipients is also limited. In Bangkok, Praditpornsilpa and associates reported that international consensus on the 2-hour postdose (C2) concentration of cyclosporine may be too high for Asian ethnic kidney transplants. Their data indicated lower-than-recommended C2 level as an appropriate C2 target concentration.[12] An Iranian study done by Assari and coworkers suggested that the optimal level of C2 might be different in ethnic populations.[13] Another Asian study revealed that proper C2 levels might be lower among the Taiwanese. They concluded that suitable C2 levels for Asians required more consideration in trials of larger sizes, because the greater part of reference levels are currently fulfilled from studies of Caucasians.[14]

It is currently blurred which dose and blood levels of cyclosporine are best with respect to immunosuppressive value and drug definite side effects at the level of individual and ethnic population.[15] As well as the lack of enough evidence, the blood level of these assays and ethnic differences, especially in Iranian kidney transplant recipients, and optimal concentration of cyclosporine blood level has not been determined so far. Therefore, a retrospective study on 1270 kidney transplant recipients was conducted to determine the ideal cyclosporine levels for therapeutic drug monitoring among Iranian patients.

MATERIALS AND METHODS

Patients

The study population included all patients receiving a first or second kidney transplant from a deceased or a living donor referred to Gholhak laboratory, a reference center for measurement of cyclosporine blood levels, from 2008 to 2010. Patients were excluded if they had a known allergy to cyclosporine or panel reactive antibodies level higher than 40% at the time of transplantation. This study protocol was approved by the Ethics Committee of Baqiyatallah University of Medical Science, Faculty of Medicine.

Cyclosporine Dosing

Cyclosporine was taken orally as a basic immunosuppressant in kidney transplant recipients. The patients were also administered mycophenolate mofetil or azathioprine and prednisolone. All transplanted patients firstly received oral cyclosporine twice daily with mycophenolate mofetil or azathioprine plus steroids. In order to prevent rejection, cyclosporine was started on with higher doses and then gradually reduced. Doses were determined by the weight of the individual and cyclosporine blood level. Dosages also differed for each individual depending on the patient's ability to withstand kidney rejection. Our target blood level for the trough levels (C0) were 200 ng/mL to 300 ng/mL during the first 3 months after transplantation, 100 ng/mL to 250 ng/mL for a period of 4 to 12 months, and 100 ng/mL to 150 ng/mL after the 1st year after transplantation. The

C2 optimum levels of 800 ng/mL to 1000 ng/mL and 400 ng/mL to 600 ng/mL were considered from 1 to 3 months after transplantation and the following months, respectively.

Cyclosporine Assay

At all study visits, the C0 and C2 blood levels were measured. Blood samples were obtained in the morning for the C0, and then recipients were asked to take their cyclosporine. Subsequently, blood was taken 2 hours after cyclosporine intake (C2). Sampling time with a deviation of ± 15 minutes was considered acceptable. Cyclosporine was measured in peripheral blood for the whole blood concentrations of cyclosporine, correspondingly. Cyclosporine levels were measured in the whole blood using the Cobas Mira-Plus Analyzer (Roche, Basel, Switzerland).

Data Collection

Kidney allograft function was evaluated by serum creatinine as well as blood urea. Age and gender of donor and recipients were also recorded.

Statistical Analyses

The SPSS software (Statistical Package for the Social Sciences, version 17.0, SPSS Inc, Chicago, Ill, USA) was used for all the analyses. Quantitative variables were expressed as mean ± standard deviation, while qualitative variables were shown as frequency and percentage. The Kolmogrov-Smirnov test showed that the C0 and C2 levels were not normally distributed; hence, nonparametric tests including the Spearman rank correlation test were used. Comparison of the cyclosporine levels and serum creatinine with regard to sex and cytomegalovirus infection was performed using the Wilcoxon rank sum test and the general linear model for regression analysis, including source of donor as a factor.

To evaluate the relationship between cyclosporine levels and serum creatinine, we performed a receiver operating characteristic (ROC) curve analysis evaluating C0 and C2 levels upon a normal serum creatinine, by gender, as predictors of kidney allograft function (serum creatinine values of at least 1.6 mg/dL for men and 1.4 mg/dL for women).[16] We calculated our final therapeutic range based on the most appropriate product of specificity and sensitivity. We also reported the target therapeutic range within the most specific and 90% sensitive values. A *P* value of less than .05 was considered significant, and 95% confidence intervals were used for analyses.

RESULTS

Demographical Setting

Medical charts of a total of 1270 kidney transplant recipients were reviewed at different transplant centers from Tehran. Overall, 4419 blood samples were obtained. The mean age of recipients was 36 ± 15 years (range, 4 to 84 years); 61.5% males and 38.5% females (Table 1). The majority of the patients received a kidney from a living donor (85.2% unrelated and 8.1% related living donors), while 6.3% of patients received a deceased donor graft. The mean age of the donor was 28 ± 6 years (range, 6 to 64 years); 82.6% were males and 17.4% females. The demographic and baseline variables of these patients are shown in Table 1. A total of 1174 patients (92.6%) completed the follow-up period for more than 1 year, while 45 patients (3.5%) were followed up for 3 to 12 months and 49 individuals (3.9%) for less than 3 months.

Receiver Operating Characteristic Curve Estimation

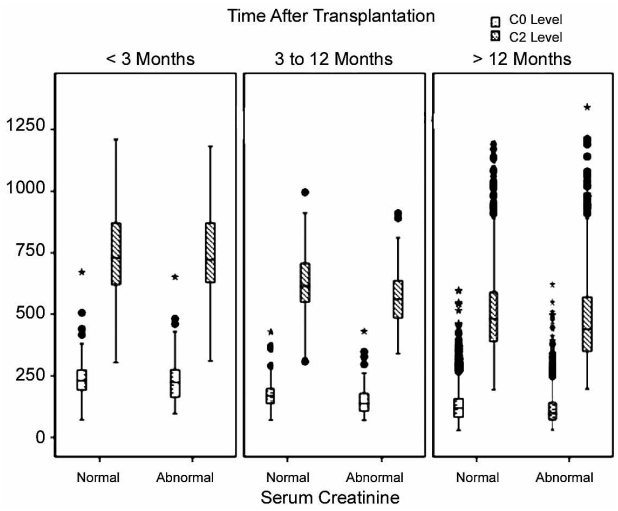
In the subset of patients with creatinine values of at least 1.6 mg/dL for men and 1.4 mg/dL for women, C0 and C2 indexes were good discriminators between therapeutic and nontherapeutic serum creatinine ranges (normal creatinine based upon

Table 1. Baseline Characteristics of Patients*

Variable	Value
Number of patients	1270
Age of recipient, y	36 ± 15
Age of kidney donor, y	28 ± 6
Male donor, %	82.3
Donor source, %	
Deceased	6.3
Living	93.7
C0 level, ng/mL	
Months 0 to 3	237 ± 85
Months 4 to 12	168 ± 64
After 12 months	133 ± 80
C2 level, ng/mL	
Months 0 to 3	752 ± 168
Months 4 to 12	609 ± 126
After 12 months	508 ± 181

*C0 indicates the through level of cyclosporine in blood and C2, the 2-hour postdose level.

gender versus abnormal creatinine levels; Figure). In this subset, the area under the ROC curve for C0 and C2 were 0.542 and 0.498 ($P = .29$ and $P = 0.77$), respectively. The ROC curve area overalls for C0 and C2 in different time after transplantation are demonstrated in Table 2. The optimal recommended target levels of C0 and C2 levels in various times after transplantation is also shown in Table 2.



Box plots for cyclosporine levels categorized by serum creatinine ranges. C0 indicates the through level of cyclosporine in blood and C2, the 2-hour postdose level. The solid line is the median; dotted line, mean; and whiskers, 10th and 90th percentiles.

Associations of Cyclosporine Levels With Serum Creatinine

Finally, we performed a general linear model regression analysis calculating the hazard as a function of age, sex, and donor type. A significant relationship was found between serum creatinine and cyclosporine levels; after adjustment for the covariates, the effect of C0 and C2 on creatinine was diminished. Female sex, age greater than 35 years, and deceased donor source increased probability of abnormal serum creatinine (Tables 3 to 5).

Table 3. Mean Target Levels of Cyclosporine by Gender at Different Times After Transplantation*

Cyclosporine	Male Patients	Female Patients	*P*
C0 level, ng/mL			
Months 0 to 3	260 ± 128	223 ± 119	
Months 4 to 12	173 ± 73	163 ± 76	
After 12 months	142 ± 91	145 ± 93	< .001
C2 level, ng/mL			
Months 0 to 3	741 ± 165	769 ± 168	
Months 4 to 12	603 ± 133	616 ± 117	
After 12 months	515 ± 185	527 ± 187	< .001

*C0 indicates the through level of cyclosporine in blood and C2, the 2-hour postdose level.

Table 2. Optimal Recommended Target Levels of Cyclosporine After Transplantation Based on Receiver Operator Characteristic Curve*

Cyclosporine	Best Product of Specificity and Sensitivity	90% Specificity	Area Under Curve	*P*
C0 level, ng/mL				
Months 0 to 3	230 – 240 (639 to 591 – 471 to 511)	362.5	0.567	< .001
Months 4 to 12	135 – 156 (763 to 610 – 489 to 620)	205	0.639	< .001
After 12 months	95 – 120 (648 to 485 – 479 to 619)	193.5	0.575	< .001
C2 level, ng/mL				
Months 0 to 3	725 – 775 (518 to 426 – 488 to 407)	1017	0.489	.77
Months 4 to 12	535 – 612 (780 to 503 – 380 to 326)	745	0.64	< .001
After 12 months	420 – 479 (654 to 529 – 534 to 422)	680.5	0.564	< .001

*C0 indicates the through level of cyclosporine in blood and C2, the 2-hour postdose level.

Table 4. Mean Target Levels of Cyclosporine by Donor Source at Different Times After Transplantation*

	Kidney Transplant Recipients by Donor Source			
Cyclosporine	Deceased	Living Related	Living Unrelated	*P*
C0 level, ng/mL				
Months 0 to 3	264 ± 129	259 ± 86	271 ± 121	
Months 4 to 12	188 ± 106	134 ± 40	175 ± 73	
After 12 months	154 ± 91	164 ± 115	143 ± 90	< .001
C2 level, ng/mL				
Months 0 to 3	782 ± 162	682 ± 96	745 ± 161	
Months 4 to 12	572 ± 121	569 ± 120	609 ± 120	
After 12 months	508 ± 180	542 ± 206	501 ± 177	< .001

*C0 indicates the through level of cyclosporine in blood and C2, the 2-hour postdose level.

Table 5. Mean Target Levels of Cyclosporine by Age at Different Times After Transplantation*

Cyclosporine	Age < 35 y	Age ≥ 35 y	*P*
C0 level, ng/mL			
Months 0 to 3	291 ± 132	224 ± 92	
Months 4 to 12	186 ± 87	154 ± 58	
After 12 months	145 ± 87	145 ± 97	< .001
C2 level, ng/mL			
Months 0 to 3	759 ± 172	741 ± 154	
Months 4 to 12	606 ± 117	579 ± 117	
After 12 months	509 ± 180	503 ± 182	< .001

*C0 indicates the through level of cyclosporine in blood and C2, the 2-hour postdose level.

The C0 and C2 data were stratified by serum creatinine therapeutic ranges: nontherapeutic (abnormal serum creatinine for each gender) and therapeutic (normal serum creatinine for each gender). Significant differences in levels of C0 and C2 were noted between all C0 and C2 therapeutic ranges.

DISCUSSION

Investigation of the best immunosuppressive drug is essential in kidney transplantation, and research in this field continues. Greater decrease in calcineurin inhibitors' dose is associated with a better maintenance of kidney function.[4] Also, the incidence of cardiovascular problems, malignancies, and chronic allograft nephropathy suggests reduction of cyclosporine dose. However, cyclosporine dose reduction seems to be linked to elevated incidence of acute rejection.[17] Immunosuppressive regimens based upon low doses of cyclosporine may improve short-term outcome after transplantation, but the most beneficial immunosuppressive protocol at present is not known in the Iranian population. Reduced cyclosporine exposure offers equivalent protection of kidney function compared with the standard dose of cyclosporine after kidney transplantation and does not result in under-immunosuppression.[18]

We found that our average C0 and C2 levels were lower than other studies,[19,20] like other Caucasian and Asian studies. In addition, clinical data regarding the cyclosporine dose reduction in Iranian kidney transplant recipients is limited. There are some reports in close proximity to this study. In Bangkok, Praditpornsilpa and colleagues reported that international consensus for C2 concentration might be too high for Asian ethnic kidney transplant patients. Their data illustrated lower than suggested C2 level as a proper C2 optimal concentration.[12] The recommendation states achieving the recommended target level of about 1700 ng/mL within 3 to 5 days after kidney transplantation that must be reduced thereafter.[21] In another study, the mean value for C0 level was about 250 µmol/L.[22] Although C0 has less value,[23] in few studies that are available it is higher than that of our study and more than 850 ng/mL.[22,24,25] An Iranian study performed by Assari and associates suggests that the optimal level of C2 may be different in ethnic populations.[13] Another Asian study reveals that appropriate C2 levels may be lower among the Taiwanese.[14]

Even with new achievements in kidney transplantation, African-American kidney transplant recipients continue to show poorer prognosis in long-term clinical outcome and graft survival compared to Caucasian kidney transplant recipients. The function of immunosuppressant in kidney transplantation is vital. Thus, ethnic differences in the pharmacokinetics of immunosuppressant are an answer issue in the experimental differences in kidney transplantation outcome in different ethnic population. Ethnic differences in pharmacokinetics of cyclosporine, especially in Iranian kidney transplanted on the current literature, are either absent or only of minor application. It described that cyclosporine showed evidence of ethnicity-specific differences in bioavailability and/or dose-adjusted systemic exposure. Oral bioavailability of cyclosporine in African-Americans was between 20% and 50% lower than in Caucasians, so Caucasian population get higher dose than requirements to maintain similar average concentrations of the particular immunosuppressant. Since cyclosporine undergoes extensive metabolism and are substrates for CYP3A isoenzymes as well as the drug transporter P-glycoprotein, interethnic variability in activity of these enzymes/transporters may provide a common mechanism for the observed ethnic differences. These observations are most likely produced by several nongenetic factors, such as CYP3A4, CYP3A5, and ABCB1.[26]

It seems that cyclosporine dose should be individualized in kidney transplantation.[27] With respect to the unclear dose of cyclosporine blood levels in Iranian kidney transplant recipients, we suggest our optimal doses with respect to

immunosuppressive efficacy and drug specific side effects. Several pharmacodynamic measures of cyclosporine effects have been planned, for example by respect to gender, donor sources, and age of 35 and greater, doses of drug can be adjusted in Iranian patients.[15]

Scientific evidence confirms gender differences in some specific cytochrome P450 enzymes, such as CYP3A, having elevated activity in female gender, typically in the small intestine. A 24% higher activity of CYP3A is illustrated in the liver of females than males, but it is reported that there are 200% higher differences in the CYP3A activity in small intestine of females. A study has revealed significant differences in male and female patients reveal this difference in transplanted patients.[28,29] Female gender might metabolize more cyclosporine in the intestinal mucosal cells because they have a better activity of cytochrome P450 enzymes.[30] Finally, according to these results, gender should be an essential concern when cyclosporine administrate in Iranian kidney transplant recipients in a clinical setting.

In recent years, outcome of kidney transplantation in patients older than 60 years of age is clearly enhanced. In cyclosporine scope, older patients show evidence of a higher mortality, especially from infectious and cardiovascular causes, than young patients. In a review article suggested that the immunosuppressive treatment in older patients enabled more flexibility immunosuppressive. Nevertheless, it is recommended to avoid overimmunosuppression elderly patients should be treated with lower doses and fewer immunosuppressive drugs.[31] We demonstrated it was more necessary to consider age of kidney transplantation.

The strengths of this study lies in the setting and design. The study was a population-based cross-sectional study. The suggested C0 and C2 levels were based on the large numbers of patients from multi center clinic referred to a single laboratory. The use of data from only one laboratory reduced the possible confounding effect of differences in the access to C0 and C2 level. Validated measures were used to assess the drug blood levels of the study groups. The limitation of the study is the misclassification according GFR, the classification of chronic diseases and reasons for encounter was based on information in the medical records. Creatinine, however, is not a sensitive test for predicting the kidney function in the study. The estimated GFR based on one of the formulas and creatinine clearance are better choices for this purpose. However, we did not calculate GFR in our study because of lack of data. Also, using date-stratified graft survival can result in better findings.

CONCLUSIONS

It seems that the current recommended cyclosporine levels are high for Iranian kidney transplant recipients population. We recommend our cyclosporine doses for Iranian kidney transplant recipients be adjusted according to age, sex, and donor source. Due to the practical limitations, better quality evidence from well-designed randomized trials with longer follow-up periods is required before lower blood level of C0 and C2 can be recommended.

CONFLICT OF INTEREST

None declared.

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Received March 2011
Revised March 2012
Accepted April 2012