Satisfactory Outcome Despite Low 2-Hour Postdose Cyclosporine Level in Iranian Kidney Recipients

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Introduction. Cyclosporine has a narrow therapeutic serum level in kidney transplantation. Achieving the recommended therapeutic levels is necessary, but in different ethnic groups, the impact of the cyclosporine level on patient and graft survival has not been fully addressed yet. We investigated this issue by studying the 2-hour postdose serum concentration of cyclosporine (C2) and the long-term graft and patient survival in Iranian transplant recipients.
Materials and Methods. A total of 397 kidney recipients were evaluated for the C2 serum levels. All patients were under treatment with prednisolone, mycophenolate mofetil, and cyclosporine (Neoral). Measurements C2 were considered at different time intervals: the first 2 months, 2 to 6 months, and after 6 months posttransplantation. The mean of C2 levels at specified intervals were evaluated and compared with the recommended optimal ranges. Patient and graft survival rate were also calculated.
Results. In the studied patients, C2 levels were lower than the upper recommended range in 96.9%, 83.6% and 64.5% in the first 2 months, between 2 and 6 months, and after 6 months posttransplantation, respectively. The overall 5-year patient and graft survival rates were 95% and 85%, respectively.
Conclusions. Despite the fact that the majority of the patients had C2 levels lower than the recommended values, we observed good patient and graft survival rates. Our data suggests that different populations may need different target levels definition.

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INTRODUCTION

Cyclosporine A has a narrow therapeutic window and requires blood level monitoring.[1] Extensive data has shown that 2-hour postdose cyclosporine blood level (C2) is the best single measure for monitoring the therapeutic level of cyclosporine.[2-5] In 1998, and international consensus conference proposed its target C2 levels to enhance the clinical outcome of kidney transplantation.[2] However, a number of recent studies have demonstrated that these recommendations are not precise, or at least there may be differences in optimal cyclosporine levels between different kidney recipient populations.[6,7]

In our country, one study showed that the initial administered doses are lower than the recommended values.[8] To the best of our knowledge, no study has ever evaluated C2 blood levels of the Iranian kidney recipients in comparison to the recommended levels of the international consensus conference. In this multicenter study, we aimed to retrospectively evaluate C2 blood levels in our kidney transplant recipients at different times after transplantation along with short-term and long-term patient and graft survival rates.

MATERIALS AND METHODS

In a retrospective design, we used data from the reference laboratory for cyclosporine measurement after kidney transplantation in Tehran, Iran. The laboratory receives patients from transplantation centers in Tehran. Data regarding C2 measurement for patients who underwent kidney transplantation between 2001 and 2005 in 3 major transplantation centers in Tehran (Shaheed Labbafinejad, Baqiyatallah, and Shaheed Hasheminejad hospitals) were extracted. Then, we included those patients who have at least 1 follow-up C2 measurement at the following intervals after transplantation: less than 2 months, 2 to 6 months, and more than 6 months. The other patients were excluded. We then contacted the relevant transplantation centers and private or hospital-based outpatient follow-up clinics for the latest data on graft and patient survival. We excluded those patients with unknown outcomes.

The Immunosuppression strategy included triple therapy with prednisone, mycophenolate mofetil, and microemulsion formulation of cyclosporine (Neoral, Novartis, Basel, Switzerland). Cyclosporine was given in equally divided doses twice a day at approximately 12-hour intervals. For adjustment of cyclosporine dose, after reaching the recommended values based on C2 level (800 µg/L to 1200 µg/L),[1,4] the patients were followed according to the through level of serum cyclosporine concentrations (C0) for prevention of nephrotoxicicity.

We used the SPSS software (Statistical Package for the Social Sciences, version 13.0, SPSS Inc, Chicago, Ill, USA) for Microsoft Windows to analyze the data. The relative frequency of the study population which were in-range and out-of-range for the C2 level in each time interval after transplantation were reported.[1,4] We also evaluated patient and graft survival rates in different periods using the Kaplan-Meier method.

RESULTS

Among all the reviewed patients, 397 kidney recipients met the inclusion criteria and entered the study. From these, 246 (61.9%) were men and 151 (38.1%) were women. The mean age of the patients at the time of transplantation was 36.0 ± 15.5 years. The sources of kidney allografts were living unrelated donors in 338 (85.1%), living related donors in 43 (10.8%), and cadavers in 16 (4.0%) cases.

The mean follow-up duration was 33.3 ±18.7 months. Of the study population, 385 (96.9%) in the first 2 months, 332 (83.6%) between 2 and 6 months, and 256 (64.5%) after 6 months posttransplantation had their C2 levels below the target ranges (mean values, 933 ± 260 µg/L, 881 ± 256 µg/L, and 745 ± 197 µg/L, respectively). The C2 levels were never within the recommended range in 227 patients (57.1%), and 39 (0.9%) had C2 levels in the recommended range at all measurements.

The overall graft survival rate for 1, 3, and 5 years were 95%, 88%, and 85%, respectively. The overall patient survival rate for the specified periods were 98%, 96%, and 95%, respectively.

DISCUSSION

The present study revealed good overall patient and graft survival rates for our patient population despite obvious lower blood levels of C2, compared to the consensus recommendations.[1] We found that in 57% of our patient population, C2 levels never met the target levels in all their posttransplant measurements that were studied. Our results corroborate the findings of a large number of recent studies that disputed the target levels declared. In a German study, the authors reported C2 values lower than the recommended levels in 68% of their total transplant population in the first 2 months posttransplantation and in 55% at late posttransplant period.[6] An Australian study also demonstrated that a C2 level of less than the recommended value on the 7th day after transplantation was associated with complete elimination of acute rejection incidence for the first month posttransplantation.[9] A French study in which they used monoclonal antibodies and antilymphocyte induction therapy for their kidney transplant recipients was indicative of good outcomes despite a low cyclosporine dose.[7] The same observation was reflected a report from Iran on the effect of adding mycophenolate mofetil to the immunosuppression therapy.[8]

One reason for these findings could be different immunosuppression protocols used in the transplant centers worldwide. Another explanation was provided by a research which demonstrated that genetic polymorphism plays a role in defining optimal initial cyclosporine dose administration in kidney transplant patients. The authors related the good outcome detected in kidney recipients

despite the lower initial cyclosporine dose to the genetic differences.[10] Moreover, these results may be the effect of high proportion of slow absorbers in whom C2 measurement is not appropriate and longer period indexes are recommended.

CONCLUSIONS

We conclude that the studied Iranian kidney transplant recipients have good outcomes despite significantly lower level of C2 compared to the recommended levels. Further studies to elucidate the mechanism for this and defining target ranges in different populations could be helpful.

CONFLICT OF INTEREST

None declared.

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