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Renal Data from Asia-Africa

Is Short Term Outcome of Iranian Renal Transplant Recipients Affected by Mean First 6 Months C2 Level?

Shervin Assari[1,2], Maryam Moghani Lankarani[2,3], Yunes Panahi[3], Behzad Einollahi[3],

[1]Medicine and Health Promotion Institute, [2]Clinical Research Unit, Baqiyatallah Medical Sciences University, [3]Nephrology and Urology Research Center, and Kidney Transplant Department, Tehran, Iran

ABSTRACT. International Consensus Conference (ICC) has suggested that the whole blood level of Cyclosporine (CsA) be kept strictly at a certain level. However, it is not well understood whether failing to maintain these levels will affect the short term outcome in different patient populations or not. We aimed to assess if the short term outcome of Iranian renal transplant recipients will be affected by first 6 months C2 level. In a retrospective cohort, 265 consecutive kidney transplant recipients were categorized as group with mean C2 lower than recommended range (mean C2 levels in the first 6 month after transplantation lower than the recommended ranges; n=213) and group with mean C2 within recommended range (mean C2 levels in the first 6 month after transplantation within the recommended range; n=52). All recipients were negative for panel reactive antibody, and had received their first (living unrelated) kidney transplantation in Baqiyatallah hospital, between 2002 and 2003. The groups were similar in characteristics and 6 months, 1, 2, and 3 years patient and graft survival rates were considered as outcome. No significant difference was observed in patient and graft survival rates between the two groups (P> 0.05). The patient survival rate in group with mean C2 lower than recommended range and group with mean C2 within recommended range were: 6 months: 98% vs. 98, 1 year: 97% vs. 98%, 2 years: 97% vs. 98% and 3 years: 97% vs. 98%. The graft survival rate in the above groups were as follows: 6 months: 93% vs. 91%, 1 year: 92% vs. 91%, 2 years: 92% vs. 77% and 3 years: 89% vs. 69%, respectively. The result of our study showed that lower mean C2 levels was not necessarily accompanied with a worse short term outcome in our patients. This finding suggests that the optimal level of C2 may be different in ethnic populations.

Introduction

Cyclosporine (CsA) has a narrow therapeutic window. Although introduction of microemulsion formulation (Neoral) has shown a good promise in reducing intrapersonal variability[1] but close monitoring with the aim of maintaining therapeutic effects as well as preventing nephrotoxicity is still necessary.[2]

International Consensus Conference (ICC) have proposed recommended C2 levels to enhance the patients' outcome based on the results of transplantation in north America,[3] but a number of recent studies from different ethnicities

Correspondence to:

Dr. Shervin Assari
Medicine and Health Promotion Institute
Tehran, Iran
E-mail: assarish@yahoo.com

have reported satisfactory outcomes in their patient populations despite having a lower C2 values than those recommended by ICC.[4,5]

A study from Iran, showed that the initial administered doses are lower than the recommended values.[6] Another recent study by Pourfarziani et al reported good outcomes despite significantly lower level of C2 in Iranian kidney transplant recipients.[7] 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 designed a retrospective cohort to investigate the short term effect of lower than recommended C2 levels on patient and graft survival rates, in Iranian renal transplant recipients.

Methods

In a retrospective cohort, we included 265 consecutive kidney recipients, transplanted in Baqiyatallah hospital, Tehran, Iran from 2002 to 2003. Inclusion criteria were receiving the first allograft from a living unrelated donor and being negative for panel reactive antibody. All recipients were under triple therapy with prednisolone, mycophenolate mofetil and cyclosporine microemulsion (Neoral). Induction immunotherapy was used in none of the patients. The groups were not significantly different in terms of donor and recipient age, donor and recipient gender, ischemia time, follow-up time, and number of HLA missmatchs.

Post-transplant immunosuppressive monitoring was done based on patients clinical status and also the serial measurements of serum creatinine, calculated creatinine clearance, liver function tests and the C2 level was not used for changing of the dose of Cyclosporin.

According to the whole blood mean C2 levels in the first 6 months after transplantation, patients were divided into two groups: group I with mean C2 lower than recommended range (n=213) [3] and group II with mean C2 within recommended range (n=52). (None of the patients represented a higher than recommended C2 level).

We then retrospectively followed the patients for a period of 3 years for patient and graft survival. 6 months, 1, 2, and 3 years patient and graft survival rates were considered as outcome and compared between the two groups.

We used SPSS version 13.0 for Windows for data analysis. Survival analysis was performed using Log-rank test. *P*-values < 0.05 were considered significant.

Results

In the study population, 178 (67.2%) were male and 87(32.8%) were female. The mean age at the time of transplantation was 37 ± 17 year. Patients in the two groups were not significantly different regarding age, sex and cause of end stage renal disease (ESRD). The groups were also not significantly different in terms of donor and recipient age difference, donor and recipient gender, ischemia time, follow-up time, and number of HLA mismatch (P >0.05).

The mean C2 level for the first six months was 801.9 ± 237.1 ng/mL in group I and 1120.2 ± 259.0 ng/mL in group II with mean C2 within recommended range.

The patient survival rate in different time intervals after transplantation in group I and group II were: 6 months: 98% vs. 98, 1 year: 97% vs. 98%, 2 years: 97% vs. 98% and 3 years: 97% vs. 98% respectively (P >0.05).

The graft survival rate in different times post transplantation in group I and group II were as follows: 6 months: 93% vs. 91%, 1 year: 92% vs. 91%, 2 years: 92% vs. 77% and 3 years: 89% vs. 69% respectively. Again, there was no significant difference between the two groups.

Discussion

According to the results of this study, having mean first 6 months post transplantation whole blood C2 levels lower than the target ranges of ICC is not essentially associated with worse 3 years patient and graft survival.

Our findings provide a higher level of evidence for previous claims regarding achieving a good patient and graft outcomes with lower

than recommended C2 levels.[2,4] Einecke et al has observed excellent long-term results with a C2 measure as low as 500-600 ng/mL,[2] and Ahmadi et al has also observed improved renal function, dyslipidemia and hypertension with such strategies.[4]

Pourfarziani by reviewing data regarding C2 measurement for patients who underwent kidney transplantation between 2001 and 2005 in 3 major transplantation centers in Tehran (Shaheed Labbaf inejad, Baqiyatallah, and Shaheed Hasheminejad hospitals) included those patients who had at least 1 follow-up C2 measurement. Good overall patient and graft survival rates were reported for the Iranian population despite obvious lower blood levels of C2, compared to the consensus recommendations. In that report, 57% of transplanted population, C2 levels never met the target levels in all their posttransplant measurements that were studied.[7]

In a study of German renal transplanted patients, in 68% C2 values were lower than the recommended levels in the first 2 months post-transplantation and in 55% at late post transplant period.[2] In an Australian transplanted study, a C2 level of less than the recommended value on the 7th day after transplantation was linked to complete elimination of acute rejection incidence for the first month post-transplantation.[8] In France, kidney transplant recipients had good outcomes despite a low cyclosporine dose.[5] The same was reported from Iran.[9]

Some factors may explain these results including different immunosuppression regimens than those at the time of publishing the guidelines may be a possible factor, as some later studies with different immunosuppression strategies[2,5] have reduced the cyclosporine dose effectively with no adverse effect on the outcomes. Differences in the pharmacokinetic parameters of cyclosporine in different patients[9] and racial and ethnic populations[8,10] may be the other contributing factors to cyclosporine metabolism and may result in different plasma cyclosporine levels due to the genetic differences.[10]

Slow cyclosporine absorbers demonstrate lower levels of C2 compared to other longer interval measures like C6.[3] While reports showed that between 10% and 20% of the patients are slow absorbers during the early post-transplant period, many of them revert over time to the normal pattern,[11] a large portion of the population (80.3%) in our study at the first 6 months post-transplantation with low C2 levels seems to have normal absorption pattern however, future studies must elucidate this.

Our study had some limitations, including small sample size and lack of long term patient and graft survival. Nevertheless, this may be the first comparative study and the hypothesis's presented should be tested in multi-ethnic groups.[12-15]

In conclusion, we found that having a mean whole blood C2 level lower than the recommendation during the first 6 months post renal transplant is not accompanied with poor short term patient or graft survival for Iranian renal transplant recipients. Further investigations for determining a more precise target range for cyclosporine blood levels in different ethnic kidney recipient populations seems to be necessary.

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