Received: 2008.06.26 Accepted: 2009.01.25 Published: 2009.03.16	Approach to a target value for 2-hours post dose Cyclosporine (C2) during the first week post renal transplantation					
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	Summary					
Background:	There is not a wide consensus on whether recommended target ranges for 2-hours post dose cyclosporine (CsA) blood level (C2) are generalizeable to all kidney recipient populations worldwide. In this study we aimed to assess in which C2 level we can obtain the least acute rejection (AR) episodes in our kidney transplanted patients.					
Material/Method:	In a retrospective cross-sectional study, we investigated all our renal recipients with at least a valid C2 blood level at the days between 5–9 post transplantation. All patients were under immunosuppressive therapy with CsA (Neoral), prednisolone and MMF.					
Results:	Hundred forty-four patients were eligible for inclusion in the study. Mean age of the study subjects at the time of transplantation was 36.8±16.6 years. 99 (69%) of the patients were male. Overall, 16 (11%) patients experienced AR during the first two weeks post-transplantation. Mean C2 blood levels for patients experiencing AR was 793±335 compared with 1028±391 for patients without AR (p=0.023). We found that none of the patients with a C2 level of higher than 1300 ng/mL experienced an episode of AR.					
Conclusions:	According to our findings, we recommend that for minimization purpose of the incident AR episodes among LURD kidney, a C2 blood level of higher than 1300 ng/mL to be obtained during the first week post-transplantation. Alongside, approaching specific C2 targets for patients with different drug regimen or genetic polymorphisms seem necessary.					
Key words	Cyclosporine C2 • C0 • target • acute rejection • immunosuppression					
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BACKGROUND

Acute rejection episodes in the early phase post renal transplantation are important clinical challenges because of their effects on short- and longterm graft and patient survival [1,2]. Since its introduction in the early 1980s, cyclosporine has revolutionized the practice of solid organ transplantation. Even in the newly introduced immunosuppressive protocols which use other immunosuppressive agents (eg. Sirolimus), cyclosporine still is being used especially in the early period post renal transplantation [3,4]. However, the narrow therapeutic index which has presented cyclosporine as a critical-dose drug has effectively complicated enjoying use of the agent. Hence, monitoring blood levels of the drug for prevention of its attributed side effects is of extreme importance.

Total cyclosporine exposure, estimated by the area under the blood concentration versus time curve (AUC), has been considered for some time to optimize therapy with cyclosporine and improve outcomes in renal transplant recipients [5,6]. However, determination of a full, 12-hour AUC is impractical and costly and so has not been accepted as appropriate for clinical practice. Several studies have demonstrated that dosing by monitoring the whole blood level of the drug, 2-hours post-dosing (C2) is an effective and practical way to optimize cyclosporine therapy in solid organ recipients [7–10].

In 1998, International Consensus Conference proposed definite C0 and C2 target ranges to achieve, to optimize clinical outcome [11]. But it is not well understood whether failing to maintain these serum levels will affect the overall outcome in all kidney recipient populations with different characteristics. A large number of recent studies have demonstrated that these recommendations are not precise or at least there may be some disparities in optimal CsA levels between different kidney recipient populations [12]. In a previous study (unpublished), we demonstrated that in Iranian kidney transplant recipients, the allograft would remain in a good condition despite failing to achieve the proposed C2 values. In this study we aimed to investigate whether there is any specific C2 or C0 levels for the early post transplantation period, through which Iranian Kidney transplant population would be effectively saved from acute rejection episodes.

MATERIAL AND METHODS

Patients and study design

In a multi-center retrospective cross-sectional study, we investigated all our renal recipients with at least a valid C2 blood level at days between 5-9 post transplantation and a concomitant serum creatinine value. All 144 patients were under triple immunosuppressive therapy with cyclosporine microemulsion formulation (CsA-ME; Neoral, Novartis Pharma, Basel, Switzerland), mycophenolate mofetil (MMF, Cellcept®, Roche Pharmaceuticals, Sydney Australia) and prednisolone. We extracted the following data from our transplantation departments' data registry: age, sex, C2 blood level at the days between 5 and 9 post-transplantation and concomitant C0 levels, and acute rejection (AR) episodes. In 30% of the cases, diagnosis of the AR was confirmed with allograft biopsy and the reminder were determined clinically, as two consecutive serum Creatinine >2 mg/dL or a 1.5 fold rise in serum creatinine level confirmed with another laboratory evaluation 48 hours later. One of the patients was recipient of second kidney allograft. Other characteristics are listed in Table 1.

Statistical analysis

For evaluating patients within AR and non-AR groups regarding their cause of ESRD, gender and "in range" and "out of range" C0 and C2 blood levels, we used Pearson Chi-square test and Fisher's exact test. Independent sample t test was used for assessing potential differences between patients with and without AR episodes in their mean C0 and C2 blood levels, first Creatinine measures, cyclosporine daily doses and age at the time of transplantation. Two sided P<0.05 were considered significant.

RESULTS

Demographic and study findings are presented in Table 1. Hundred forty-four patients were eligible for enrollment into the study. Mean age of the study subjects at the time of transplantation was 36.8 ± 16.6 years ranging from 4 to 82 (15% < 19 yr). 99 (69%) of the patients were male. The causes of kidney failure were: glomerulonephritis (n=25), diabetes mellitus (n=16), urologic complications (n=8), polycystic kidney disease (n=6), congenital disorders (n=3), and SLE (n=1). Overall, 16 (11%) patients experienced AR during the study period. There was no significant difference between pa-

	Allograft status				F statistics	Cirr (2 toiled)		
	Acute rejection			Normal		Sig. (2 tailed)	lotal (%)	
Cyclosporine daily dose	396.	88±136.58*	400.	74±99.93	4.30	0.889	400.	31±104.05
C2 (2-h post dose cyclosporine)	793.18±335.35		1027.94±391.04		0.940	0.023	1001.86±391.25	
C0 (cyclosporine trough level)	247.18±156.50		281.93±130.76		1.205	0.406	278.07±133.69	
First Creatinine level	3.05±1.15		1.22±0.33		89.097	0.000	1.42±0.75	
Age at transplantation	33.56±16.08		37.25±16.71		0.378	0.405	36.84±16.63	
Gender (male)	12	(75.0%)	87	(68.0%)		0.776	99	(69.0%)
Patients with C2 >1300 ng/ml	0	(0.0%)	33	(26.0%)		0.022	33	(23.0%)
Patients within C2 target range (%) [#]	0	(0.0%)	16	(12.5%)		0.217	16	(11.0%)
Patients with $CO > target range (\%)^{##}$	11	(69.0%)	111	(87.0%)		0.072	122	(85.0%)
Cause of ESRD						0.202		
Diabetes mellitus	2	(12.5%)**	14	(11.0%)			16	(11.0%)
Hypertension	2	(12.5%)	12	(9.0%)			14	(10.0%)
Glomerulonephritis	2	(12.5%)	23	(18.0%)			25	(17.0%)
Urologic	1	(6.5%)	7	(5.5%)			8	(5.5%)
Congenital	1	(6.5%)	2	(1.5%)			3	(2.0%)
Polycystic kidney	0	(0.0%)	6	(4.5%)			6	(4.0%)
Lupus (SLE)	1	(6.5%)	0	(0.0%)			1	(0.5%)
nephrotic syndrome	0	(0.0%)	2	(1.5%)			2	(1.5%)
Unknown	7	(44.0%)	62	(48.5%)			69	(48.0%)
Total	16	(11)***	128	(89.0%)			144	(100.0%)

Table 1.	. Measured	variables in (our patient r	opulation re	aarding stat	e of their kidne	v allograft.
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* Mean ±SD; ** number (percent) within each group; *** number (percent) of total population; # 1700 ng/ml ±20%; # 150–300 ng/ml.

tients with AR and without AR episodes in their age, sex and cause of renal failure (p>0.1). Mean C2 blood levels for patients experiencing AR was 793±335 compared with 1028±391 for patients without AR (p=0.023). We found that none of the patients with a C2 level of higher than 1300 ng/mL experienced an episode of AR.

DISCUSSION

The critical importance of achieving adequate cyclosporine exposure during the early days post transplantation to prevent acute rejection has been documented in several prospective studies. However, cyclosporine has an erratic gastrointestinal absorption profile and as previously mentioned, is of high inter- and intra-individual absorption variability; Hence, because of the critical dose nature of the agent and extreme importance of preventing nephrotoxicity alongside the AR during the early post-transplantation period, it would be sound to define a clear-cut lower limit for a safe C2 level as well as an upper limit, in order to expand the therapeutic target ranges.

To address the abovementioned issue, an International Consensus Conference [11], with regard to the findings of the clinical trial Monitoring of 2 h Absorption in Renal Transplantation (Mo2art) [13,14], proposed a minimum C2 target of 1700 ng/ml to be reached during the early days post renal transplantation. A number of other studies focusing on the outcomes of kidney recipients with "in-range" and "out-of-range" C2 levels have also reported similar results to the Mo2art trial. However, these studies endpoints were usually concerned with acute rejection, and the risks for nephrotoxicity usually underregarded. Considering the results of these studies, one can assume that the higher the C2 levels



Figure 1. First Creatinine measures and concomitant C2 blood levels in studied kidney transplant recipients.

are, the less rejection you get. But this advantage must also be confronted to toxicities, drug intolerance, and over –immunosuppression.

The present study results suggest that for achieving highest outcomes with lowest early AR episodes, attainment of a cyclosporine blood level of at least 1300 ng/ml for the second 5 days post renal transplantation is adequate. Indeed most values in our study fell within: 500–1500 ng/ml over the 2nd 5 days post-transplantation (Figure 1).

Achieving a surprising lower target limit for C2 levels during the early period post renal transplantation, our study observation contrasts the recommendations of the International Consensus Conference. Corroborating to our findings, some other studies from other parts of the world have also reported that their patients when monitoring on other exposure indices and generally represent a low incidence of AR, had also lower C2 levels compared to the target C2 values proposed by the International Consensus Conference [11]. For example, in an Australian study using AUC(0-4) for monitoring cyclosporine, Morris et al. found that the mean C2 level of patients without AR episodes was 963±133 ng/ml (vs. 793±205 ng/ml in AR group); and the incidence of rejection during the first month was 0% when C2 exceed 1200 ng/ml at day 7 [15]. In another study conducted in Germany, it was revealed that in long-term transplantation period, patients who did not represent a recent acute rejection episode had mean C2 level of 551±203 ng/ml which was quiet lower than recommended value (800 ng/ml) [16]. Moreover, Loichot et al. in a survey on a French kidney transplant population, where patients were monitored based on C0, found that during the first 2 months

post transplantation, 68% of the population did not meet proposed C2 values; and only about 45% of the study population reached the proposed C2 range in long-term follow up [17]

But how can we explain these phenomena? Loichot et al. [17], as well as another study [13], related these differences to unalike drug regimens in North American therapeutic strategies at that time. An Italian study also confirmed that patients using MMF in their immunosuppressive regimen reach to the peak level of cyclosporine blood concentration faster (hour 1 vs. hour 2 post dosing in control group on EC-MPS) [18]. An Iranian survey proposed genetic polymorphism as a major factor in defining optimal initial cyclosporine dose given to renal transplant patients [19]. They related the good outcome detected in the studied kidney transplant population despite the lower administered initial cyclosporine doses, to their genetic characteristics. Alongside, we know that in delayed absorbers, C2 level does not represent the maximum cyclosporine blood concentration after dosing; thus, one may suppose that some of these results may be due to a potential higher proportion of delayed absorbers in specific populations.

In our study population, patients received triple immunosuppressive therapy using cyclosporine, prednisolone and mycophenolate mofeti (MMF) concomitant with diltiazem as a CsA-sparing agent. Our results may be justifiable to a part because of using MMF in our drug regimen. However, MMF nowadays is widely used in kidney transplant patients worldwide, and even some of the studies using this agent haven't report such an observation. On the other hand, it may be presumed that use of a CsA-sparing agent can explain this; but Morris et al. have engendered doubts about it when they found no significant affect of DTZ on relations between outcome and CsA pharmacokinetics [15].

CONCLUSIONS

The present study revealed a relatively good outcome for our patient population despite obvious lower levels of cyclosporine 2-hours post dose (C2) compared with International Consensus Conference recommendations. According to our findings, we recommend that to adequately estimate CsA dose adjustment given to LURD different kidney transplant populations, prospective studies with large study populations to be designed to evaluate the potential influences of ethnic and genetic differences, immunosuppressive protocols, and other potential interfering factors in defining definite C2 target ranges during the different phases post transplantation.

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