Cyclosporine trough Level or 2-hour Postdose Level Monitoring Among Kidney Transplant Recipients: Iranian Practice

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Dear Editor,

Several randomized multicenter studies and single-center trials have evaluated cyclosporine 2-hour postdose (C2) monitoring within a range of regimens in various organ transplantations, providing a robust evidence base for the benefits of this sensitive monitoring technique.[1] Although, there are consensus statements on benefits of C2 blood level, the quality of studies in this area is poor, and the practical limitations of C2 monitoring mean that further evidence is required before a strategy for the administration of cyclosporine based on C2 levels can be recommended.[2] However, it seems that C2 has priority than cyclosporine trough (C0) level.[2,3] We conducted a national retrospective study to assess the approach of cyclosporine monitoring at 24 kidney transplant centers of Iran, between 2008 and 2011. In this study, 34 547 cyclosporine level measurements from 7706 kidney transplant recipients were enrolled. The majority of them (n = 34 472) had C0 level and 22 532 (65%) had also C2 blood levels measured. All cyclosporine blood levels, from either inpatients or outpatients, were measured in a single laboratory. These selected target tests were aligned to standard local practices for each transplant center. The results showed that C0 blood level was more popular and requested test for adjustment of cyclosporine doses compared to C2 blood level by Iranian transplant physicians.

Although C2 blood level has the priority for drug monitoring compared to C0 blood level,[4] there were increasing trend for C0 blood level monitoring in Iranian nephrologists practices.[5,6] It seems there are several reasons for that. First, only one blood sample is usually obtained for the measurement of all routine biochemical tests plus C0 level in the morning. However, C2 blood level measurement requires the second blood sample. Thus, two blood samples should be taken from each patient. Second, the disadvantages for C2 blood level measurement are mainly centered on patients' compliance and tolerance. Blood samples are usually obtained in the morning for the biochemical routine tests, and then recipients are asked to take their cyclosporine. Subsequently, blood is taken 2 hours after cyclosporine intake for C2 level determination interrupts working time during the day. In fact, it can cause noncompliance problems and C2 blood level sample is going to be missed. Third, C2 monitoring has practical disadvantages which must be considered. Because blood samples for C2 values are obtained during a more dynamic phase of cyclosporine absorption than those for C0 blood levels, precise timing of samples is crucial. Consensus guidelines suggest that there is a 10-minute "window of opportunity" before and after the 2-hour point during which samples should be taken.[2] Fourth, in spite of the general belief that the area under the curve pharmacokinetic monitoring provided a reliable way for actual drug exposure, superior to C0, in clinical practice therapeutic drug monitoring of cyclosporine with C0 values continued to be used, mainly because of simplicity. To date, only little data from prospective studies are currently available to support the clinical benefits of C2 levels monitoring. In addition, further evidence is required for clinical implication of C2 monitoring because the quality of these studies is poor.[2] In a study, lower C2 level is not necessarily associated with a worse short term outcome in kidney transplants.[7] In addition, Pourfarziani and colleagues showed that although most of the kidney recipients had C2 levels lower than the suggested ranges, they observed good patient and graft survival rates.[8] Thus, unreliability of C2 blood level and simplicity of C0 level monitoring are the main causes of the decreased practical popularity of C2 level monitoring among Iranian transplant nephrologists. On the other hand, unreliability of cyclosporine blood levels monitoring resulted in blood samples were collected to monitor cyclosporine levels (C0

and C2) simultaneously in 65% of patients.

In conclusion, the present study showed the increased usage of C0 blood level assay for cyclosporine monitoring in Iranian nephrologists practice. However, we are waiting to find a faster, simpler, less expensive, more practical, and more accurate method of cyclosporine assays.

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Re: Risk Factors Profile and Cardiovascular Events in Solid Organ Transplant Recipients

Dear Editor,

I read with great interest the review article recently published in the *Iranian Journal of Kidney Diseases* titled "Risk Factors Profile and Cardiovascular Events in Solid Organ Transplant Recipients" by professor Ghods.[1] This review focused its message on drawing the attention of the high prevalence of risk factors and cardiovascular events after organ transplantation, especially in kidney transplant recipients. According to this review, the prevalence of cardiovascular disease risk factors increases or remains higher after kidney transplantation. The cardiovascular risk factors in these patients divide into traditional and nontraditional risk factors, which immunosuppressive agents categorized as a traditional risk factor.[1] They may cause posttransplant diabetes mellitus, dyslipidemia, hypertension, and hyperhomocysteinemia, and studies involving withdrawal of these agents have generally shown improvement in parameters such as blood pressure and dyslipidemia.[2]

Traditional risk factors do not adequately explain coronary heart disease risk after kidney transplantation.[3]Immunosuppressive agents could also play role as a nontraditional risk factor for cardiovascular events. They have potentially a direct adverse influence on the immunologic protective mechanisms in atherosclerosis. It was shown that a number of protective immune responses have also been identified. For example, one of the most important of these is carried out by the regulatory T cells, which are powerful inhibitors of atherosclerosis in several mouse models.[4] Regulatory T cells inhibit the development of autoimmunity by controlling the activity of autoreactive T cells. If the function of regulatory T cells is compromised in hypercholesterolemic mouse models of atherosclerosis, the development of disease becomes much more aggressive.[5] In addition, immunization of hypercholesterolemic animals with low-density lipoprotein (LDL) preparations reduces atherosclerosis, suggesting