



## Cyclosporine monitoring in organ transplantation: Do we need a new concept?

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Exact monitoring of cyclosporine, as one of the main important medications in organ transplantation, can prevent from rejection or drug toxicities. Reading this article is recommended for nephrologists who are involved in the transplantation medicine.

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Although the introduction of cyclosporine (CyA) in the 1980s as maintenance immunosuppressive regimen in solid organ transplantation (1) revolutionized this field, the therapeutic drug monitoring (TDM) of CyA to optimize efficacy and safety is still of clinical interest. During last 3 decades, no consensus has been attained yet on the criteria to derive benefit from the immunosuppressive efficacy, while limiting the side effects of CyA (2). As in clinical experiences, no relationship could be found between administered doses and clinical effects, fixed doses of CyA were not the best way to use the drug. To avoid side-effects, therefore, monitoring of CyA blood level is mandatory to modify the individual doses of the drug. CyA exposure, as calculated by area under the curve (AUC), has been shown to correlate with clinical outcomes in kidney transplant recipients (3). In Pharmacokinetic studies, the level obtained just before the next dose known as trough level (C<sub>0</sub>) has demonstrated a poor correlation with both CyA exposure and the development of acute rejection and nephrotoxicity (3). On the other hand, the C<sub>0</sub> target level proposed immediately after transplant period is extremely wide, ranging from 100 to 500 ng/ml (2). In fact, there is no study that has ever provided strong data correlating C<sub>0</sub> levels with the probability of rejection or toxicity, unless for the extremely below or extremely above therapeutic range of C<sub>0</sub> blood levels (4). Unfortunately, side effects can also be observed at therapeutic CyA levels among transplant

patients (2). In addition, no difference is seen between CyA blood levels during acute rejection and throughout normal allograft renal function. Thus, no therapeutic range for CyA levels could be suggested and just the extremely high levels of CyA could be correlated with toxicity (2). In clinical practice, the choice of the proper CyA dosage to reach safe and effective state is very difficult by the marked between and within patients' variability in CyA pharmacokinetics and pharmacodynamics. Pharmacokinetic fluctuating in CyA absorption, volume of distribution, and metabolism are so great that strategies based on C<sub>0</sub> blood level monitoring is not helpful for a transplant patient. However, the microemulsion formulation of CyA, Neoral, has the superior pharmacokinetics, the more complete and predictable absorption, and the decreased inter- and intra-individual variability in pharmacokinetics (2). Kahan *et al.* (1995) believe that the best estimate of CyA exposure for each recipient is the full 12-hour area-under-the concentration-time kinetic curve (AUC<sub>0-12</sub>), not C<sub>0</sub> blood level (5). Several strategies for monitoring of Neoral therapy are suggested that they include from 1 point (concentrations at 0, 1, 2, 3, or 4 hours) and 2-point samples, (C<sub>0</sub> - C<sub>1</sub>, C<sub>0</sub> - C<sub>2</sub> or 2 and 6 hours' post-dose) through multiple-point (all five levels 0 to 4 hours or AUC<sub>0-12</sub>) predictors are used (2, 3, 6, 7). However, it is still debated. Finally, the following questions should be answered.

*Question:* What should be the target level (or range) for CyA in different kinds of organ transplant patients in the immediate, short- and long-term post-transplant periods? What is the best method for cyclosporine efficacy and safety monitoring in different types of organ transplantation and also in early and late post transplantation periods?

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On the other hand, to date CyA is treatment of choice for so many disorders such as different kinds of autoimmune diseases; hence:

**Question 2:** What is the best measure for CyA efficacy and safety monitoring among non-transplant patients? Moreover, pharmacokinetic studies have recommended that CyA levels at 2 hours post-dose (C2) is the best way to predict AUC in kidney transplants. In addition, C2 blood values correlated with acute rejection episodes and nephrotoxicity better than C0 blood levels (3). C2 monitoring has practical disadvantages which must be considered. Because blood samples for C2 values are obtained during a more dynamic phase of CyA absorption than those for C0 blood levels, precise timing of samples is crucial. Consensus guidelines suggest that there is a 10-min "window of opportunity" before and after the 2-hr point in which samples should be taken (7). Therefore, in spite of the general belief that the AUC pharmacokinetic monitoring provided a reliable way for actual drug exposure, superior to C0, in clinical practice TDM of CyA 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 (7). In a study, lower C2 level is not necessarily associated with a worse short term outcome in kidney transplants (8). In addition, Pourfarziani *et al.* showed that although the most of the kidney recipients had C2 levels lower than the suggested ranges, they observed good patient and graft survival rates (9). However, following questions should be considered.

**Question 3:** Could we wish to find a faster, simpler, less expensive, more practical and more accurate method of CyA assays? In spite of CyA nephrotoxicity, it can cause several side effects such as development of diabetes mellitus, dyslipidemia, hyperkalemia, hyperuricemia, hypertension, cardiovascular morbidity, hirsutism, gingival enlargement and malignancy (1, 3, 10, 11). Furthermore, most studies have analyzed the relationship between CyA blood levels versus acute rejection episodes and nephrotoxicity. There are some conflicting evidence and few reports as to whether CyA-related side effects are dose dependent phenomena (3).

**Question 4:** What are target CyA levels to minimize long term (such as malignancy, gingival hyperthrophy, hirsutism) and short term side effects while maintaining adequate

immunosuppressive effect to avoid acute organ rejection? Which of cyclosporine side effects are dose dependent?

CyA has a narrow therapeutic window with variable absorption characteristics, even with Neoral, requiring close monitoring to ensure adequate immunosuppression (3, 10). Variability in CsA absorption is more prominent during the first week following kidney transplantation.

**Question 5:** What is the best matrix, feasible tool and the optimal desired Neoral concentration?

Wacke *et al.* in 2006 declared that simultaneous pancreas-kidney transplant patients show relevant differences in CsA pharmacokinetics (6).

**Question 6:** Are there actually any differences in CsA pharmacokinetics in different types of organ transplantation?

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