

A Systematic Review about an Advance in Cyclosporine Monitoring in Kidney Transplant Recipients

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Abstract

Context: An immunosuppressive drug, Cyclosporine (CsA), has been commonly used in kidney transplants. A safe dosing of CsA often causes nephrotoxicity, bone marrow toxicity, and infection. Pharmacokinetic characteristics of CsA and CsA marker relation to the immune suppression have not been completely described in clinical practices yet.

Objectives: This review summarizes our achievements on pharmacokinetic and CsA level Marker in kidney transplant patients.

Search methods and Selection criteria: A literature review was done using the National Center for Biotechnology Information's Pubmed Medline, Ovid Medline and Embase, and Iranian registries (Iranmedex, SID, MagIran, and IranDoc). Titles and abstracts were then reviewed to select studies based upon the predefined inclusion criteria. Our study defined a population of adult solid organ transplant recipients receiving the cyclosporine that Cyclosporine monitoring was done.

Data Collection and Analysis: Two reviewers independently appraised the quality of each trial and extracted the data from the included trials.

Results: CsA pharmacokinetics is very different between kidney transplant recipients, in order to CsA profiling, no pharmacodynamic tools has been confirmed yet in clinical practices and the best way to individualize calcineurin inhibitor therapy is still a controversial issue. C0 levels do not exactly predict the CsA level or rejection risk, patient monitored by C2 levels have upper doses of CsA and have a lower frequency of early acute allograft rejection than patients profiled with C0 and although CA is highly heterogeneous closely post-transplant and seems to be unhelpful early after post-transplant it is more favorable after first months after.

Conclusions: Establishing a biological CsA marker may be helpful in clinical decisions on the dose. It seemed to be logical that we should re-inspect the possibility of using them as a supplementary tool towards better therapeutic drug monitoring of cyclosporine or it needs to be reevaluated and needs to find a new target for a therapeutic plan in kidney transplant patients.

Keywords: Cyclosporine, Monitoring, Kidney Transplant

1. Context

Cyclosporine A (CsA) is an immunosuppressant drug extensively used in organ transplant patients to reduce the rejection rate. At first this drug is isolated from the fungus *Tolypocladium inflatum* isolated from a soil sample obtained by Sandoz scientists at Hardangervidda, Norway in 1969 (1). Cyclosporine is a cyclic nonribosomal peptide of 11 amino acids and contains a single D-amino acid, which are rarely encountered in nature (2). The immunosuppressive effect of CsA was discovered on 1972. The success of CsA in preventing organ rejection was shown in kidney transplants by Calne (3) and in liver transplants performed by Starzl et al. (4). CsA bind to the cytosolic protein cyclophilin of immunocompetent lymphocytes, particularly T-lymphocytes. This complex of cyclosporine and cyclophilin inhibits Calcineurin, which, under normal circumstances, is responsible for activating the transcription of interleukin 2. Calcineurin then dephosphorylates the transcription factor NF-AT (nuclear factor of activated T-

cells), which moves to the nucleus of the T-cell and increases the activity of genes coding for IL-2 and related cytokines. Cyclosporine inhibits the dephosphorylation of NF-AT by binding to cyclophilin (5). It also inhibits lymphokine production and interleukin release and, therefore, leads to an increase in function of effector T-cells. It is believed that CsA cause its effects by directly binding to the cyclophilin D protein that constitutes part of the mitochondrial permeability transition pore and by preventing the Calcineurin phosphatase pathway (6-8).

Ever since the discovery of CsA, graft failure with acute rejection incidence has decreased and patient survival enhanced (9). The Calcineurin inhibitors (CNIs), especially CsA, have had a great effect on the overall achievement of kidney transplantations favorable outcome and CsA is the most important immunosuppressive drug currently used for kidney transplants (10). CsA is the base of many immunosuppressant practices all around the world. Therapeutic monitoring of the CsA is important due to the fact

that this drug has a constricted therapeutic range with severe probable side effects. Nonetheless after close observation, significant sets of transplant patients have acute rejection or CsA nephrotoxicity in spite of the CsA blood level upkeep within the recommended dosage, which is different in any center (11, 12). For example CsA nephrotoxicity is a major reason for chronic kidney dysfunction. Accurate dosing of CsA is key because of the need to adequate blood level of CsA for avoiding kidney rejection; in a slim therapeutic level in this patient group. In count, exact dose administration of CsA and its nephrotoxicity are the 2 other issues related to CsA (13) that can be an independent hazard issue for graft loss and mortality after kidney transplantation. Furthermore, mortality outcomes from cardiovascular disease, infection, and malignancies are important reasons for CsA, which this drug can cause indirectly (14). Therefore, the search for an optimal CsA dosage continues to be essential (15). Although, the best evident clinical marker of CsA effectiveness is the measurement of kidney function and graft histology and the individualized treatment targets can be based on the patient's and his graft's medical history (16), however it is interventional and seems to not be practicable. However, CsA level observing is essential (17).

Best CsA level achievement in kidney transplant recipients is tough because of inconsistency in CsA metabolites and ethnic factors (18). Furthermore, to this there are some other basic problems in field of CsA monitoring; the main concern is analytical method for CsA measurement. Currently, there are 6 analytical techniques for CsA monitoring and numerous are in advance (19-21). These analytical methods vary in their accuracy and specificity, and it showed that the 2 methods can be as much as 57% different in average or can be much larger, depending on such factors as transplant type, the time after transplantation, and liver function (22).

Second; CsA concentrations in extracellular or whole-blood fractions is different and measurement of whole-blood or extracellular blood concentrations does not necessarily offer an exact and reproducible image of intracellular CsA level within T cells. For example, CNIs in whole blood are highly bound to erythrocytes and lipoproteins. However, inter- and intra-patient differences of these structures have been shown to affect CNI concentrations in lymphocytes (23, 24). Evidence supports the theory that T-cell suppression is the key mechanism by which CNIs achieve immune suppression therefore T cells are interesting candidates for pharmacodynamics-monitoring tools (25).

Third; there are many confounding variables such as meals, patients who take CsA with meals sometimes or at fasting may have change in CsA blood level, which could result in to under- or overdosing (26).

Another factor that could pointedly disturb CsA blood level is the CsA transporters, similar to most immunosuppressive drugs that have substrates for one or more drug transporter proteins; such as P-glycoprotein, that are expressed on T cells (24, 27). Intracellular CsA absorptions can consequently be changed by cellular drug-exporting activities. Pharmacokinetic outlines and drug-drug interactions at this level are not monitored by current CsA level measurement. To more accurate level determination, intracellular T-cell drug concentration assays have been established (28). CsA levels are used as a replacement marker of kidney function, but do not certainly display a relationship with pharmacological response (29).

2. Methods

This review aimed to evaluate the cyclosporine A monitoring in patients who underwent kidney transplant. We intended to the best method for cyclosporine A monitoring. More specifically, this review intended to answer the following relevant questions:

1. Is cyclosporine A monitoring effective in kidney transplant?
2. What cyclosporine A monitoring method in conventional methods are best?
3. What is new about cyclosporine A monitoring?

2.1. Criteria for Considering Studies for This Review

2.1.1. Types of Studies

Randomized clinical trials comparing the addition of cyclosporine A to standard treatment in kidney transplant patients. Trials were included irrespective of publication status, language, and blinding.

2.1.2. Types of Participants

Adult kidney transplant patients (18 + years of age).

2.1.3. Types of Interventions

Intervention: Cyclosporine A was considered, regardless of the mode of administration.

2.1.4. Types of Outcome Measures

The number of patients with kidney transplants who treated with cyclosporine A monitoring was used as the outcome measure of interest. The definition of suppression was based on the modified vilko (30). The primary outcome asses' best monitoring method that preserving transplanted kidney. Secondary outcome measures included: 1. the number of deaths; 2. the number of patients who raised creatinine; and 3. adverse events. Adverse

events included: 1. any serious adverse events that were fatal, life-threatening, or requiring inpatient hospitalization or prolongation of existing hospitalization with regard of monitoring methods; 2. any adverse events that resulted in significant disability or in capacity; 3. any important medical events that might not be immediately life-threatening or resulted in death or hospitalization, but might jeopardize the patient or required intervention to prevent one of the above outcomes with regard of monitoring methods; and 4. any adverse events that required discontinuation of medication with regard of monitoring methods.

2.2. Search Methods for Identification of Studies

A literature review was done using the National Center for Biotechnology Information's Pubmed Medline, Ovid Medline and Embase, and Iranian registries (Iranmedex, SID, MagIran, and IranDoc). Search terms were broad and equivalent for each database, specifically for literatures studying Cyclosporine trough level or Cyclosporine 2 hours post dose blood level monitoring in adult human solid organ transplantation from 1970 up to now. Preliminary search results were reviewed for duplication. Titles and abstracts were then reviewed to select studies based upon the predefined inclusion criteria. These defined a population of adult solid organ transplant recipients receiving the cyclosporine, in which a Cyclosporine monitoring was done.

3. Results

3.1. C₀ Value

First suggested tools for CsA blood level monitoring was the determination of trough levels (C₀) (17). The oldest tools of CsA blood level monitoring, the C₀ level is commonly used even to date (31-33). Although it seems C₀ is useful to predict CsA side effects (34, 35), the use of C₀ is led to debates. C₀ did not closely reveal the drug dose and blood levels varied even in inter and intra individually. Changes in dose need frequent testing after to guarantee its detection. Consideration of the delay should help in the modification of doses (36). Some researcher commented that CsA trough level had no direct relation with CsA side effects and it is not an appropriate tool for drug side effects assessment (37). Hegazy SK showed CsA trough levels increased during bacterial and fungal infections and returned to pre-infection levels once the infection was resolved (38). It has long been accepted that the results of C₀ checking are suboptimal, and litterateurs in field of transplantation about C₀ has shown that area under the concentration-time curve (AUC_{0-12h}) and C_{max} (maximum concentration) have more beneficial relations with

the sufficiency or toxicity occurrences than C₀ (17, 39), C₀ monitoring does not necessitate narrow a therapeutic window as C₂ monitoring and may lead to unnecessary dosage adjustments and cause in over or under dosage underestimation (40-42). However, it seems that the overall C₀ level shows only a weak correlation with rejection (43, 44).

3.2. Why Use C₂ Monitoring in Kidney Transplantation Patients?

After that, CsA 2-hour post-dose level (C₂) monitoring has been stated to be greater beneficial in predicting consequences (17). In a Consensus suggested C₂ monitoring is the best single time-point predictor, which is the greatest inter individual variability of CsA pharmacokinetics and the best alternate for C_{max}, and which agrees with the period of maximal Calcineurin inhibition (17, 39). However, evidence of C₂ monitoring in stable renal transplant patients is limited. Most of this finding comes from studies that there are not clinical trials and most of them assess switching method C₀ to C₂ (32, 45-47). However, the technique is more critical, but immunoassay bias is lower with C₂ than with C₀ (31). Pharmacokinetic monitoring of C₂ quickly has changed from experimental pharmacology to routine clinical practice. These techniques have now been extensively validated, and appear to offer important and immediate therapeutic, in most clinical policies all over the world (48). Approvals for use of C₂ monitoring for clinical treatment were established to be furthermore reviewed (17, 49). The clinical advantages of C₂ profiling are not limited to Kidney transplantation, but use to all solid organs so far transplanted (50) for example in a study showed that prospective comparison has established a highly significant correlation between C₂ and AUC₀₋₆ in liver transplantation (51). An international multi center randomized trial has been definite that acute rejection is lower in transplanted kidney recipients monitored by C₂ than C₀ levels (52). In maintenance liver and heart recipients, Cantarovich and colleagues (13, 53) have shown a beneficial effect of C₂ than C₀ in relation of AUC₀₋₄ (54).

CsA possibly will increase (55) or decrease (56) drug blood level by the induction or inhibition of metabolic enzyme. In-vitro studies have shown that the concentration of CsA within the dosing interval is in reverse correlation to lymphocyte Calcineurin activity or IL-2 production (40, 57). The maximum inhibition of these parameters happens 2 hours after dosing, with the peak concentration of CsA in peripheral blood. One caution concerning the C₂ values assayed is although may not always be evaluated most effectively (58).

Data regarding C₂ profiling prospectively examined risks and benefits are rare in renal transplant recipients. Experience with C₂ monitoring in maintenance patients are little, a study established that an satisfactory C₂ level

soon after transplantation is accompanying with a decreased risk of acute rejection in adult renal transplant recipients not in maintenance phase. In the maintenance phase, although mean C2 levels do not seem to identify patients at risk of rejection, it may help to identify too much immunosuppression and improve long-term survival by decreasing CsA toxicity (59).

For cyclosporine C2 monitoring, blood should be drawn within 15 minutes of the 2-hour post dose time point (26) that any delay may cause bias in level estimation. On the other hand there are studies that revealed that in C2 monitored patients, C2 levels are not predictive for the incidence of early allograft rejection (60). However, more studies showed that C2 relates with AUC0-4 in kidney transplanted patients (61), as has been reported in heart (53, 62) and liver (13) transplantation, although this correlation can be impaired by concomitant administration of Diltiazem (63).

3.3. C Max and 3-Hour Cyclosporine Blood Level Monitoring

Some study suggest that cyclosporine blood level after 3 hours may represent a better method of monitoring cyclosporine dose than cyclosporine trough blood level. Cyclosporine blood level 3 hours after renal transplantation is closely associated with acute rejection and cyclosporine nephrotoxicity (64). The highest concentration of CsA (C max) is believed to reveal the time point of maximal Calcineurin inhibition in response to CsA (49, 65, 66). To our knowledge there is little study to show a correlation of a C max and 3-hour CsA blood level monitoring post-dose CsA concentration with acute rejection and nephrotoxicity in kidney transplant recipients. CsA blood level after 3 hours may be a better tool than cyclosporine trough blood level. However, safety and efficacy require a formal prospective randomized study (64). C max and 3-hour cyclosporine blood level have their limitation like meals confounding factor, for example, meals can decline the Cmax and AUC of CsA (67, 68).

3.4. Area Under the Curve Monitoring

There has been a different method of therapeutic drug profiling for optimizing CsA dosing in kidney transplant recipients, however, it showed that whole exposure to CsA, as reflected by the area under the concentration-time curve (AUC), was a better outcome predictor than single point (trough) CsA blood level (17). To provide a more exact CsA level monitoring, AUC used in different times after dosing, however, the most valuable AUC timing for CsA is AUC0-12 (69). Restricted AUC of CsA like AUC 0 - 6 after CsA administration have shown to improve clinical outcomes, especially than single point (51, 61, 64). CsA AUC for 0 - 4

hours (AUC0-4) also offers valuable information regarding the CsA blood level (10, 69). A study established that CsA blood level for AUC0-4 allied well with the entire AUC 0-12. However, a study showed AUC0 - 4 and C0 levels correlated poorly with AUC 0 - 12 (70) against other studies that showed AUC0-4 accompanied with better clinical results (61, 71). However, the area under the curve of blood CsA level versus time is a better monitoring tool than CsA point profiling (72, 73).

Although AUC can be assessed CsA exposure better with stronger power for outcome prediction has a limited sampling approach (74-76), it seems clinical application is impracticable, and it wants several blood sampling (10, 69) also, another problem is the costs related with sampling and analysis (64). However, it showed that levels above the threshold of about AUC 0 - 4 are desirable to minimize the risk of rejection (77) and seems because the difference in CsA is highest in AUC 0 - 4 (58). Some new research showed some estimators able to predict cyclosporine AUC0-12h in patients using only 3 blood with minimal bias and may be combined to increase the reliability of CsA dose adjustment in routine (78).

3.5. Relative Importance of Attaining Cyclosporine Absorption

The CsA absorption (C2/C0 or CA) phase is important for inhibition of the T-cell and it relates to the concentration of the CsA move in T cells (79). Differences in CA have an important effect in preventing nephrotoxicity (79) CA is effected by small intestine absorption, and it showed that CYP3A4 and PGP activity over time post-transplant changes (80) and CA may change and be in control of CYP3A4 and P-glycoprotein (81-85). CA varies greatly and immediately after transplantation and CsA absorption increases throughout the first 2 weeks (77). It showed that mutual use of C0 and C2 may have beneficial for CsA profiling because interprets both the absorption and the elimination phase (79) and some study suggested C2/C0 ratio. Mutual use of C2 and C0 as a CA profiling have better efficacy than C0 alone (59, 86).

Some study concluded that it's better to start absorption profiling to prevent any nephrotoxicity and It declared that the mixture of C0 and C2 (C2/C0 or CA) provided good correlation with AUC 0-12 (70). However, literatures in this field are rare and seems that Pharmacodynamics policies and Prospective Randomized clinical trials is needed to be designed to address this question. Results of an analysis indicate that CsA monitoring with CA throughout the early post-transplant phase reduced the risk of rejection than C0 alone like other trials in stable renal transplant patients (45, 53, 87) heart (53, 54), liver (13, 88), and lung (89, 90) transplant recipients. Twin use of C2 and C0

offers furthermore evidence for dosing decisions, mainly throughout the early post-transplant period (91).

3.6. Individualizing Target Range and Adjusting Dose of Cyclosporine

Kidney transplant recipients show clinical variation in response to CsA, it presumed some proteins are involved in charge that called CNI binding proteins immunophilins. It suggested that the nuclear factor of activated T-cells (NFAT) reduce after Calcineurin inhibition; genetic polymorphisms in the encoding NFAT genes could also be reasons for variation in CsA efficacy and toxicity. Also, CsA metabolites and their different organ delivery may possibly be another reasons (92). Additionally, enzymes are responsible; the most important enzyme in CsA hepatic metabolism is cytochrome P450 3A4 (93). It showed that a CsA level is mainly influenced by CYP3A4, CYP3A5 and MDR-1 genes. Patient's differences in clinical response recognized to SNPs in these genes, homozygous mutant patients for CYP3A5 and MDR-1 gene SNPs respond to CsA with lower CsA dosing (94). Although CYP3A5*3 difference is in some different degree, and influence on C₀ and CsA daily dosing, it seems genetic variation has little effect on the acute rejection rate in kidney transplant recipient (95). Environmental combined genetically factors also play an important role; literatures have shown that vitamin D may up-regulate the expression of the CYP3A4 gene and patient vitamin D low levels is highly in need of on sunlight and show excessive geographical and seasonal inconsistency (93). It revealed that sensitivity to CsA has inter-individual difference, and is higher in transplant recipients than in normal controls. While the molecular description for finding is not comprehended, it seems to be isolated from genetic (96). Very different genetic markers such as HLA, POR*28 allele, ABCB1, NFKB1, and many more genotypes (97-99) play a great role in disease and CsA level (98, 100), which seem to be of clinical significance. Therapeutic CsA monitoring is still need to adjust CsA dosing after administration of individualized doses (18) also time, other medication and sex differences in cyclosporine pharmacokinetics and ABCB1 gene expression in mononuclear blood cells in African American and Caucasian renal transplant recipients has great impact on CsA blood level that attenuate significance of individual therapy (101-103). Some data suggests more attention to genetically like NFAT (104) Sommerer C showed NFAT-monitoring has the potential to support pharmacokinetic monitoring during the early post-transplant period (105), however, others like Moes says that dose individualization of Cyclosporine A based on CYP3A4*22 is not indicated (106). Altogether individual therapy such as the NONMEM (107) model might be helpful.

4. Discussion

In conclusion, optimized CsA monitoring is very important to reach acceptable blood levels with reducing the risk of unbeneficial episodes such as allograft dysfunction (105, 108), CsA pharmacokinetics is very different between kidney transplant recipients, mainly in patients with different kidney disease etiologies (109) such as race, different sex, etc. In order for CsA profiling, no pharmacodynamics tools have been confirmed yet in clinical practice (110) and the best way to individualize Calcineurin inhibitor therapy is still a controversial issue. Despite severe assess for improving graft consequence by CsA monitoring policies, acute rejection events and side effects cannot be prevented (111). C₀ levels do not exactly predict CsA levels or rejection risk (77), patients monitored by C₂ levels have upper doses of CsA and have a lower frequency of early acute allograft rejection than patients profiled with C₀ (60) and although C₂ is highly heterogeneous closely post-transplant and seems to be unhelpful early after post-transplant it is more favorable after the first months after transplantation (77), however, none of them do not take in account genetically environmental factors and may be useless in predicting allograft function. Establishing biological CsA markers may be helpful in clinical decisions on the dose (111). It seemed to be logical that we should re-inspect the possibility of using them as a supplementary tool towards better therapeutic drug monitoring of cyclosporine or it needs to reevaluate and find new targets for a therapeutic plan in kidney transplant patients (112).

Although pharmacokinetic and pharmacodynamics CsA profiling has improved over the past few years, clinical evidence is poor, CsA monitored on C₂ have become the basis of immunosuppression in most countries early post-transplant and in first months after transplantation CA may have an more important role in CsA monitoring after early post-transplant period, allied with very low rejection rates. These tools could probably be enhanced additional by the means of more attention to genetically and environmental factors and results in treatment personalization in kidney, before such monitoring can be reached, more evidence is needed. Persistent studies should also be done for an improved degree of knowledge regarding CsA pharmacogenetics and pharmacodynamics in order for better drug monitoring (113).

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