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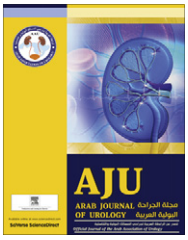

**RENAL/TRANSPLANTATION**

**REVIEW**

# The over-exaggerated chronic nephrotoxicity of calcineurin inhibitors

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**ABBREVIATIONS**

CSA, cyclosporin A; CNI, calcineurin inhibitor; AZA, azathioprine; MMF, mycophenolate mofetil; CKD, chronic kidney disease; AR, acute rejection

**Abstract** ***Background:*** Late kidney allograft failure remains a major problem in kidney transplantation. While there is no doubt that acute nephrotoxicity from calcineurin inhibitors (CNIs) exists, chronic CNI nephrotoxicity has been the subject of much debate in the transplant community.

***Methods:*** We identified original articles related to the use of CNIs in renal and extra-renal solid-organ transplantation, to examine the available evidence about their chronic nephrotoxicity.

***Results:*** There is clearly a lack of firm evidence for the role of CNIs as a major injurious agent causing chronic renal dysfunction and allograft failure. Moreover, recent evidence shows that the pathological lesions typically linked to chronic CNI use are not specific. A growing body of evidence shows that alloimmunity is a much more important cause of late renal allograft failure.

***Conclusions:*** More research should focus on addressing the true causes of chronic graft dysfunction rather than continuing to propagate the exaggerated contribution of CNIs to late graft loss.



## Introduction

With the introduction of cyclosporin A (CSA) in the 1980s, kidney transplant recipients have achieved excellent short-term outcomes, but long-term outcomes have

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not improved in parallel, and that remains hard to explain [1]. The nephrotoxicity of calcineurin inhibitors (CNIs) has been incriminated in hampering long-term kidney allograft survival [2]. Moreover, CNI nephrotoxicity was described to be almost universal at 10 years, even in grafts with excellent function [2]. The transplant community has focused its efforts on research to compare minimising CNI use, withdrawal or avoidance, and to find new immunosuppressant substitutes for CNIs, to limit their nephrotoxicity and therefore, presumably, improve long-term graft survival.

The CNIs in current clinical use include CSA and tacrolimus. The choice between tacrolimus and CSA is largely based on the transplant programme or physicians' preferences, as well as the side-effect profiles of each medication that are individually tailored to kidney transplant recipients. Of note, tacrolimus is the main CNI in use in the USA, in combination with mycophenolate mofetil (MMF) and steroids. This combination has been associated with lower acute rejection (AR) rates [3]. While CNIs have gained a reputation for causing chronic nephrotoxicity, to date there are no prospective randomised trials affirming their nephrotoxicity as a cause of graft loss. Most of the evidence comes from observational studies, which carry an inherent potential for large confounding biases. Of interest, comparing different eras of immunosuppression, specifically comparing recent CNI-sparing protocols with more than three decades of CNI use, should be interpreted with caution.

## Acute vs. chronic CNI nephrotoxicity

There is no doubt that acute CNI nephrotoxicity exists. Many of the side-effects of the CNIs surrounding their nephrotoxicity stem from the very early developmental phase of CSA, and later with tacrolimus use. CNIs constrict the afferent arterioles, causing fluctuations in glomerular perfusion and an increase in serum creatinine level. This vasoconstriction is dose-dependent and is reversible [4,5]. Chronic CNI toxicity has been highly debated as a main cause of late renal graft dysfunction and/or loss. Thus, the focus has shifted to investigate the use of sirolimus and other new immunosuppressant agents, with the ultimate aim of withdrawing or avoiding CNIs altogether in solid-organ transplantation. This shift was at the expense of studying other more important causes of late allograft dysfunction. Moreover, the existing data do not support the existence of chronic CNI nephrotoxicity. In fact, the removal of CNIs usually results in lower serum creatinine levels, mainly due to the removal of the afferent arteriole constriction, resulting in an increase in GFR. This does not necessarily have an effect on the chronic histological changes in the allograft. It has been speculated that any potential advantage of maintaining a better GFR is probably annulled by the deleterious effect on allograft function due to the higher rate of rejection with CNI withdrawal [6].

## No histological lesions are specific for CNI nephrotoxicity

The effects of chronic CNIs in kidney allografts assessed in protocol biopsies are the impetus for much controversy. In fact, there are no prospective randomised studies showing that late allograft dysfunction is due to CNI toxicity. Moreover, randomised trials have actually shown no long-term benefit to CNI-free immunosuppression (as discussed below). Nankivell et al. [2] attributed the chronic changes in renal allografts (high-grade arteriolar hyalinosis with lumenal narrowing, increasing glomerulosclerosis, and additional tubulo-interstitial damage based on protocol biopsies) to the chronic use of CNIs. Those authors also reported that the prevalence of these lesions continue to develop over time and are almost universal at 10 years, even in allografts with excellent early histological findings [2]. However, the study by Nankivell et al. lacked a control group and the biopsies were from a cohort of 120 recipients with type 1 diabetes mellitus, all but one of whom had received simultaneous pancreas-kidney transplants. Furthermore, all were bladder-drained pancreas-transplant recipients who are prone to interstitial fibrosis and tubular atrophy of the kidney allografts, based on urinary reflux, rendering those results hard to apply to recipients of a kidney transplant only. What is intriguing in this study is that the 10-year death-censored graft survival rate was 95.2% with the use of CNIs. Chronic CNI nephrotoxicity does not hold true in later studies. Based on protocol biopsies, Naesens et al. [7] showed that AR episodes and exposure to low tacrolimus levels were independent risk factors for the development of chronic pathological lesions in allografts at 1 year after transplantation, suggesting that rejection and immune-mediated mechanisms remain important in the early progression of chronic allograft pathology. The exact and exclusive contribution of CNIs alone to the development of chronic pathological lesions in the renal allograft and their role as predominant contributors to failure of the allograft over time is not clearly determined. In a recent study, Snanoudj et al. [8] retrospectively compared 48 kidney-transplant recipients who received CSA and 93 who did not. All patients in that study underwent protocol biopsies at 3 months, 2 and 10 years after transplantation. The authors reported that the histological lesions commonly attributed to chronic CSA nephrotoxicity (i.e. glomerulosclerosis, interstitial fibrosis, tubular atrophy, arteriolar hyalinosis, and fibro-intimal thickening) were not sufficiently specific to definitively diagnose CNI nephrotoxicity [8]. Moreover, Snanoudj et al. [8] found that arteriolar hyalinosis (the pathological lesion considered specific for CNI toxicity) was more frequent and more severe in the CNI group (92% of patients at 10 years) but also present in 65% of patients who never were exposed to CNIs. This adds further evidence that there are no specific histological lesions for chronic CNI toxicity [9].

## CNI use and kidney dysfunction in extra-renal solid-organ transplants

Renal dysfunction remains a major challenge after solid-organ transplantation, and is associated with increased morbidity and mortality rates. By examining the available data on chronic CNI nephrotoxicity in non-renal solid-organ transplant recipients, no firm evidence can be found linking kidney dysfunction to the chronic use of CNIs. The initial report of CNI nephrotoxicity was by Myers et al. [10], who reported that long-term CSA use in heart-transplant recipients can lead to irreversible renal dysfunction. Notably, the targeted trough CSA levels in that study were very high, at 300–350 ng/mL. Ojo et al. [11] examined the cumulative incidence of chronic kidney disease (CKD) in a large cohort of different solid-organ transplant recipients, and the use of CNIs was associated with an increased relative risk for kidney dysfunction but was not found to be a risk factor for CKD in a multivariate analysis. It is likely that CNIs play some role in kidney injury during and after solid-organ transplant, but they do not seem to be the sole cause of CKD [12]. Many other previous and subsequent studies in different solid-organ transplants reported that CNI use was not the only factor causing CKD, and in fact there was a variable contribution of CNIs in such kidney injury [13–21]. There is a wide range of CNI target levels that clinicians maintain in different non-renal solid-organ transplants, which could explain the disparity in the role of CNIs in the incidence of CKD in those studies, and might add to the challenge of interpreting their results, and the true contribution of CNIs in renal dysfunction after solid-organ transplantation.

## Different CNI-sparing protocols

Due to the continued belief in the chronic nephrotoxicity of CNIs, many trials have been carried out to assess the minimisation, avoidance or complete elimination of CNIs. The earlier reports of the use of CSA or tacrolimus with sirolimus to minimise the use of CNIs showed a lower incidence of AR than with the regimen of CSA, azathioprine and glucocorticoids [22]. Many other reports showed that the use of sirolimus in combination with CNIs is associated with inferior graft survival and renal dysfunction compared with CSA or tacrolimus with MMF and corticosteroids, due to possible potentiation of CNI nephrotoxicity by sirolimus [23–27]. Thus the combination of CNIs with sirolimus is now generally considered in patients on an individualised basis.

## CNI elimination protocols

CNI elimination basically withdraws CNIs from transplant recipients who have been on CNIs. CNI withdrawal and replacement with sirolimus were evaluated in many trials and the reported results were mixed. The main trials include the CONCEPT study [28], Spare-the-Nephron trial [29] and the CONVERT trial [30]. In the CONCEPT study there was better renal allograft function in the CNI withdrawal group, in contrast to the Spare-the-Nephron and CONVERT trials that showed no significant improvements in renal function after conversion to sirolimus at 2 years after transplantation. In the CONVERT trial, late CNI withdrawal showed no significant differences in primary safety outcomes. In fact, enrolment in the group with a GFR of 20–40 mL/min/1.73 $m^2$ was halted prematurely, because of a higher incidence of safety endpoints among the patients converting to sirolimus. Late CNI withdrawal in the CONCEPT trial was actually harmful to patients with proteinuria. The CAESAR trial [31] evaluated CNI minimisation and withdrawal strategies by randomising patients to low-dose CSA, low-dose CSA with early withdrawal, and standard-dose CSA. Renal allograft function was similar in all three groups. However, the biopsy-proven AR rate was higher in the CSA-withdrawal group but not in the low-dose CSA group.

## CNI avoidance and minimisation protocols

CNI avoidance is the omission of CNIs from a de novo immunosuppression regimen, but CNI minimisation uses CNI dose reduction to limit the presumed nephrotoxicity. In randomised prospective trials, CNI-free protocols showed no improvement in graft outcomes. The landmark ELITE-Symphony study [32] compared CNI avoidance and minimisation strategies by randomising recipients to one of four groups, i.e. low-dose sirolimus, low-dose tacrolimus, low-dose CSA, or standard-dose CSA. Renal function was better and biopsy-proven AR rates were significantly lower with low-dose tacrolimus than in all other treatment groups. Moreover, allograft survival was better with low-dose tacrolimus than with standard-dose CSA and low-dose sirolimus. CNI avoidance with low-dose sirolimus failed to show an improvement in renal function, and the biopsy-proven AR rate and graft survival were significantly worse than with low-dose tacrolimus. Importantly, the Mayo Clinic group showed that CNI-avoidance protocols have failed to show a benefit in GFR or graft histology in patients treated with sirolimus [33,34]. In a prospective and randomised trial of complete avoidance of CNIs, Larson et al [33]. compared a group of kidney transplant recipients who received sirolimus-MMF-prednisone (81 patients) to a group of patients who received tacrolimus-MMF-prednisone (83 patients) as maintenance immunosuppression, with a mean follow-up of 33 months. The 1-year patient and graft survival rates were similar in both groups ($P = 0.95$). There was also no difference in measured iothalamate GFR between the tacrolimus and sirolimus groups at 1 and 2 years. Interestingly, there was no difference in interstitial, tubular or

glomerular changes at 1 year by the chronicity Banff criteria scoring. Similar findings were reported by Hamdy et al. [35], who carried out a randomised controlled trial comparing sirolimus with low-dose tacrolimus vs. a sirolimus-based CNI-free regimen in live-donor renal transplantation. The authors found no significant differences in a chronic allograft damage index between the groups, using protocol biopsies at 1 year. The same group also reported their experience using a CNI-free immunosuppressive regimen, in a prospective randomised controlled trial [36]. Patients were randomised to a maintenance immunosuppression regimen that included steroids, sirolimus, and either low-dose tacrolimus or MMF. Recipient and graft survival rates did not significantly differ between the maintenance regimens over a mean follow-up of 5 years [36].

In the recently published Orion Study, Flechner et al. [37] randomised patients to three groups, i.e. sirolimus-tacrolimus followed by tacrolimus elimination at 13 weeks, sirolimus-MMF, and tacrolimus-MMF. The sirolimus-MMF group had a high biopsy-proven AR rate and was thereby terminated by the sponsor. The sirolimus-based regimens were associated with poorer outcomes in kidney-transplant recipients. Another randomised trial showed that conversion from tacrolimus to sirolimus at 1 month in kidney-transplant recipients on rapid steroid withdrawal does not decrease or ameliorate the progression of chronic changes in protocol biopsies during the first 2 years, even in those patients with no previous AR [38].

Looking ahead at some newer immunosuppressive agents, belatacept was approved by the USA Food and Drug Administration in June 2011 for adult kidney transplant patients who are positive for Epstein-Barr virus, and it is to be used concomitantly with MMF and prednisone. Belatacept is a novel drug in its class, a T-cell co-stimulation blocker. Two trials compared belatacept with CSA, the BENEFIT trial in recipients of standard-criteria living-kidney donor transplants [39], and the BENEFIT-EXT [40], in recipients of extended-criteria deceased-donor kidneys or those having a long cold ischaemia time. In the BENEFIT study, belatacept had similar patient and graft survival rates as CSA at 1 year after transplantation. Moreover, belatacept-treated patients had a higher measured GFR. Despite the higher incidence of early AR in the belatacept group, biopsy-proven chronic allograft changes were minimally reduced in the belatacept groups, and at 5 years there was no difference in chronic allograft nephropathy (belatacept package insert). However belatacept was associated with a higher incidence of post-transplant lymphoproliferative disorder involving the CNS in Epstein-Barr virus-negative patients. Similar outcomes were reported in the BENFIT-EXT study. Belatacept is a promising new-generation immunosuppressant agent that will find its place in solid-organ transplantation. The long-term safety profile, as well as efficacy in terms of long-term allograft survival, is far from being established. Belatacept studies need a longer follow-up to allow firm conclusions.

## Alloimmunity, and not CNI use, is the major cause of late allograft failure

Progressive renal damage from CNI nephrotoxicity has been extensively suggested, as discussed above. Its importance in causing allograft loss has been questioned. New data from the DeKAF study [41] on the aetiology of late allograft loss show that ≈57% of patients with chronic graft dysfunction have antibody-mediated injury, the mean (SD) time from transplant being 7.5 (6) years. DeKAF is a multicentre study of new-onset late graft dysfunction; patients enrolled had a kidney transplant biopsy [41]. Moreover, other groups showed that the major cause of late kidney transplant failure is antibody-mediated microcirculation injury [42,43]. In a landmark study from the Mayo Clinic group, El-Zoghby et al. [44] showed that most cases of kidney allograft loss have an identifiable cause that is not idiopathic interstitial fibrosis/tubular atrophy or CNI nephrotoxicity, and that alloimmunity remains the most common mechanism leading to graft failure. In a recent study using protocol biopsies, Hill et al. [45] reported donor-specific anti-human leucocyte antigen antibodies dramatically accelerate post-transplant progression of arteriosclerosis, and that the histological lesions mostly referred to as related to CNI chronic nephrotoxicity are mainly related to chronic antibody-mediated rejection. Moreover, Stegall et al. [46] reported that moderate to severe arteriolar hyalinosis (that has been associated with the use of CNIs) was found to a similar extent in kidney transplant recipients who were never exposed to CNIs, compared to patients treated with CNIs using protocol biopsies at 5 years after transplantation.

## Conclusion

Late renal allograft failure remains a major problem in kidney transplantation. CNI nephrotoxicity has been highly over-exaggerated as a cause of chronic allograft dysfunction and loss. A growing body of evidence shows that alloimmunity is the major mechanism leading to late renal allograft failure, and contrary to common belief, those graft losses are not attributable to CNI use. In fact, the CNI-based immunosuppression regimens remain the proven standard in kidney transplantation. Chronic CNI-induced nephrotoxicity remains controversial because there is no firm evidence of their injurious role and the non-specificity of the pathological lesions linked to their use. This makes the differential diagnosis with other immunological and non-immunological processes very cumbersome. Most of the solid

evidence available to date is against complete CNI avoidance. Presently, CNI minimisation appears to be the most effective CNI-sparing strategy. The potential risk of side-effects of CNI use should be balanced against the risk of AR, especially in patients with a high immunological risk (i.e. high allo-sensitisation, re-transplants, etc.). More research should focus on addressing the true causes of chronic graft dysfunction and loss.

## Conflict of interest

The authors have no conflicts of interest to disclose.

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