Original Article

# Calcineurin Inhibitors (Cnis) As A Maintenance Immunosuppressant For Kidney Transplantation:

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## Abstract

Kidney transplantation is the best option for patients with end-stage kidney disease. It is associated with better quality of life, lower medical costs, less hospitalization, and improved survival compared with wait-listed patients who remain on dialysis. Giving organ shortage and the rapidly growing waiting list despite local or worldwide organizations and collaboration to manage kidney organ allocation system.**4** Maintenance of a well-functioning renal graft is recently considered a must and not just an option. Because of advances in immunosuppression (IS), nowadays, one-year kidney graft survival rates is exceeding 93.59% in many centers, though long term survival is still a challenge. In this narrative review, we will list and discuss the most important aspects of a common maintainence IS drugs; calcineurin Inhibitors (CNI), its usage in renal transplantation, adverse effects, strategies to overcome those limitations by applying minimization protocols and their outcomes.

**Keywords:** Calcineurin Inhibitors, kidney transplantation.

## Introduction

The optimal Immunosuppression (IS) is administered to kidney transplant recipients to prevent rejection and allograft loss at the same time given to be given at the minimal effective dose to avoid their dangerous toxicities (Ponticelli C, 2022). The optimal regimen of both induction and maintenance therapy has not been established (Neuwirt H, 2019).

Maintainence IS drugs comprise of glucocorticoids, antimetabolites such as azathioprine, mycophenolate mofetil (MMF), enteric-coated mycophenolate sodium (EC-MPS), calcineurin inhibitors (CNI) i.e. cyclosporine A (CsA) or tacrolimus (Tac), mTOR inhibitors (mTORi) e.g, everolimus and sirolimus or the new co-stimulation blocker belatacept (Neuwirt H, 2019).

After the FDA approval of its IS properties in the field of transplantation at 1983, Cyclosporin A occupied together with the second member of CNIs, Tacrolimus, a central role. Not only in kidney or other organ transplantation, but also it was successful in varieties of autoimmune diseases. It had revolutionized the rate of graft survival without the marked myelosuppression that was common with their predecessors (Petechuk D, 2006).

As a proof of trustability and dependability, in USA there is more than 85 percent of renal transplant recipients are discharged from admission on TAC as part of their maintenance immunosuppressive regimen (Matas AJ, 2013). This is largely because TAC is more potent and associated with less rejection than other IS classes (Webster, AC, 2005). That was confirmed also in the Efficacy Limiting Toxicity Elimination (ELITE) study one and three years after

(Ekberg H, 2007), (Ekberg, 2009). Opportunistic infections such as cytomegalovirus (CMV), Epstein Barr virus, and BK viremia and nephropathy have thus became more common, and data suggest these are more common with TAC than with CsA (Hirsch HH, 2013), (Dharnidharka VR, 2009), (Leas BF, 2016)

Kidney Disease-Improving Global Outcomes (KDIGO) suggests a triple combination consisting of CNIs, antimetabolites and corticosteroids for the majority of patients. In particular, the first-line recommended triple regimen is Tac, MMF and corticosteroids (KDIGO, 2009). Tacrolimus share many characteristics as its predecessor CsA and mechanism of action as both engages, an intracellular protein of the immunophilin family, forming a complex that then engages calcineurin (Clipstone NA, 1992), to create a complex that inhibits calcineurin. The calcineurin-complex inhibits calcineurin phosphatase thus inhibit the ability of calcineurin to dephosphorylate nuclear factor (NF) of activated T cells (NFAT), required for translocation from cytoplasm to nucleus, and prevent calcineurin-dependent gene transcription (Noble S, 1995), (Peters DH, 1993) and thus disrupts the rejection development.

Despite its increased IS potency and less nephrotoxicity in comparison to CsA, TAC is also associated with more neurotoxicity and gastrointestinal side effects (Webster AI, 2005). It has also been associated with an increased incidence of new-onset diabetes (NODAT) and the development of metabolic syndrome, which are significant concerns because the main cause of death among renal transplant recipients is the cardiovascular comorbidity. (Claes K, 2012), (Almeida CC, 2013), (Leas BF, 2016). Regulatory T cells (Tregs) have been shown to be essential for immune homeostasis and graft tolerance in the field of transplantation (Sakaguchi ST, 2008), (Miroux CO, 2012). CNI was proved to cause reduction of those Tregs (Segundo DS, 2006), that may compromise long term allo-immune tolerance.

Calcineurin inhibitors (CNI) may be responsible for progressive and irreversible kidney toxicities. Nephrotoxicity is usually dose-dependent, affected by intra- and inter-individual bioavailability and metabolic genetic susceptibility. Another consideration is also how to accurately estimate drug level to avoid IS drug overexposure, as the relationship between current therapeutic drug monitoring based on blood levels and the intracellular concentration of CNI is not that linear (Naesens, M., 2009). Both levels may be unequal due to drug- drug interaction interfering with CYP450 or P glycoprotein, thus modifying their blood levels (Ponticelli, C., 2021). A study proved that up to 58% of transplanted kidneys treated with CsA and closely monitored for 10 years showed histologic signs of dose-dependent chronic nephrotoxicities, such as patchy interstitial fibrosis, arteriolar lesions, tubular atrophy, and focal, segmental, and global glomerular sclerosis due to ischemia. (Nankivell 2003). CNI arteriopathy may be presented by a preglomerular arteriole showing mucinoid thickening of the arteriolar wall and severe nodular hyalinosis, which is frequently irreversible owing to prolonged vasoconstriction. Striped interstitial fibrosis, tubular dilatation and atrophy is a characteristic feature of CNI nephrotoxicity. The causes of that changes are multifactorial in origin, resulting from an increase in free radicals (Miroux, C), an upregulation of TGF-b (Sakaguchi) leading to epithelial to mesenchymal transition , or an activation of the renin-angiotensin-aldosterone (RAAS) system with an increase in aldosterone (Zand MS 2005). Other tubular lesions are seen and include isometric tubular vacuolization and inclusion bodies due to an increase in lysozymes and giant mitochondria. The main glomerular lesions include global glomerulosclerosis due to ischemia or FSGS secondary to hyperfiltration injury (Zand MS 2005) (Azzi JR, 2013).

Many mechanisms for CNI nephrotoxicities were suggested, including an imbalance between vasoconstrictive and vasodilatory mediators as a cause of it. That is likely due to significant impairment of endothelial cell function resulting from decreased production of vasodilating prostaglandin E2 and nitric oxide, increased production of thromboxane A2 and endothelin in the afferent arteriole (Lanese DM, 1993) (De Nicola L, 1993), and increased expression of other vasoconstrictors as angiotensin II, endothelin-1, and leukotrienes (Ponticelli C., 2022). This leads to an acute reduction in renal blood flow (RBF), which is reversible after CNI dose reduction or drug cessation. CNIs are also associated with the acute development of de novo thrombotic microangiopathy (TMA) resulting in AKI, hemolytic anemia, and thrombocytopenia (Azzi JR, 2013).

Nowadays, initial doses of CsA and TAC do not exceed 3–5 mg/kg/day and 0.1 mg/kg/day, respectively. That figures were only about the third of their past values at the time of initial drug use (Ponticelli C, 2022).

High CNI exposure can also lead to systemic effects, including arterial hypertension, dyslipidemia, glucose intolerance, hyperuricemia, indirectly affecting kidney allograft function.
(Ponticelli C, 2022).

| | SRL | CyA | Tac | MMF | Aza | Pred |
|---|---|---|---|---|---|---|
| Nephrotoxicity | – | ++ | ++ | – | – | – |
| Hypertension | – | + | + | – | – | + |
| Dyslipidaemia | +++ | ++ | + | – | – | + |
| Diabetogenic | – | + | +++ | – | – | ++ |
| Hyperuricaemia | – | + | + | – | – | – |
| Neurotoxicity | – | ++ | + | – | – | + |
| Anaemia | + | – | – | + | + | – |
| Leucopaenia | + | – | – | + | + | – |
| Thrombocytopaenia | + | – | – | + | + | – |
| Skin and gums | + | ++ | – | – | – | + |
| Osteoporosis | – | + | + | – | – | ++ |
| GI upset | + | – | – | +++ | – | – |

SRL, Sirolimus; CyA, ciclosporin A; Tac, tacrolimus; MMF, mycophenolate mofetil; Aza, azathioprine; Pred, prednisolone.

**Table (I):** Spectrum of common adverse effects of maintenance IS drugs and their relatively different presentation (Ghanta M., 2013). The relatively different adverse effects profile between CNI drugs (table) allowed most transplantation programs exploit the strengths of both tacrolimus and cyclosporine - depending on the risks in individual patients and the IS toxicity profile - to optimize graft immunosuppression while avoiding - as possible - their adverse effects.

Several potential therapies have been considered in an attempt to prevent or reverse the cascade of effects resulting from CNI-induced arteriolar vasoconstriction. Calcium channel blockers (CCBs) are generally considered first-line antihypertensives immediately following kidney transplantation and may be beneficial in combating the vasoconstrictive effects of CNIs (Ponticelli C, 2022).

**Hypertension**

Hypertension is associated with adverse short-term and long-term allograft outcomes and can lead to increased morbidity and mortality post-transplant (Kasiske BL, 2004). CNIs raise blood pressure and cause hypertension through multiple mechanisms, it activates the renin–angiotensin system and deactivates the atrial natriuretic peptide, leading to arteriolar vasoconstriction with consequentially reduced GFR and extra-cellular fluid expansion (Curtis, J.J, 1994). The mechanisms also includes tubular salt reabsorption, peripheral vasoconstriction, and the sympathetic nervous system. Kasiske et al. found that a 10-mmHg increment above 140 mmHg in systolic blood pressure was associated with a 12% relative risk for graft failure and 18% relative risk of death. On the other hand, good blood pressure control may prevent many cardiovascular and kidney complications (Kasiske, B.L, 2004). Modifying lifestyle behavior and physical activity is essential to control hypertension. Calcium channel blockers reduce systemic vascular resistance acting on vascular smooth cells and may protect one from CNI-induced vasoconstriction. Renin– angiotensin system (RAS) inhibitors control arterial hypertension, reduce proteinuria (Rump LC, 2000), (Ponticelli C, 2022).

**CNI- New Onset Diabetes after Transplantation (NODAT)**

Although FK use is associated with lower kidney allograft rejection rates when compared to CsA, FK has been associated with a higher incidence of NODAT (Webster A, 2005) (Li Z, 2015). In addition to CNI use, risk factors for the development of NODAT include increased body mass index (BMI), planned maintenance corticosteroid use, hepatitis C virus infection, cytomegalovirus (CMV) infection (Ghisdal L, 2012), vitamin D deficiency and use of other IS drugs e.g. Steroids or mTORI (Pontecelli, 2022). Interestingly, CNI-induced hypomagnesemia, which is more common with FK than CsA, was shown to be an independent risk factor for the development of NODAT (Van Laecke SV, 2009). CNIs interfere with NFAT signaling in pancreatic b-cells, as they do in T-cells, thus decreasing insulin secretion (Heit JJ, 2006). CNI also can increase insulin resistance (Chakkera, H.A.; 2017), (Li Z, 2015), and

has direct toxicity on β cells (Rodriguez-Rodriguez A.E, 2019). Conversion from Tacrolimus to Cyclosporine A improves glucose tolerance in HCV-Positive renal transplant recepients in a small prospective, single-center study (Handisurya, 2016).

**Dyslipidemia**

Both CsA and Tac are associated with impaired lipid metabolism, with CsA having a more profound impact (Badiou S, 2009). Abnormalities of the lipid profile include increased total cholesterol, low density lipoprotein cholesterol (LDL-C), non-high density lipoprotein cholesterol (nonHDL-C), triglycerides, apolipoprotein B and apoO-III (Akman B, 2007). Cyclosporine increases total cholesterol (C), VLDL-C, and LDL-C by downregulating LDL receptor expression, despite hypercholesterolemia being significantly less frequent in RTRs receiving TAC with respect to CsA (Vincenti F., 2002).

Management of immunosuppression induced dyslipidemias is typically similar to that observed in the general population. The 2013 K/DOQI Guidelines consider kidney transplantation a cardiovascular risk equivalent (KDIGO, 2013). Statins are recommended for all patients with kidney transplants and is considered first-line pharmacotherapeutic options and remain the backbone of dyslipidemia management post-transplant for their proven benefits in reducing major adverse cardiovascular events (Riella LV, 2012).

**Gingival Overgrowth & Hair Growth**

GO is more commonly linked to CsA use a synergistic relationship has been shown between CsA and dihydropyridine CCBs in the development of GO (James JA, 2000), (Bharti V, 2013). CsA and FK have opposing effects on hair growth. Hypertrichosis associated with CsA may be related to inhibition of NFAT in follicular keratinocytes, (Gafter-Gvili A, 2003) and PO CsA has even been reported for the treatment of alopecia areata (Ferrando J, 2003). Conversely, FK is associated with the development of alopecia (Tricot L, 2005).

**CNI Neurotoxicity**

Between 10%-28% of patients who receive the immunosuppressant cyclosporine (CsA) experience some form of neurotoxic adverse event. Both sensorial and motoric functions may be adversely affected, and thus patients present with a wide range of neurological and psychiatrical disorders. CNI Neurotoxicity affects both the central and peripheral nervous systems.

Mild symptoms are common and include tremor, peripheral neuropathy and neuralgia (Bechstein WO., 2000). In some cases the headaches may be severe and recurrent Severe additional symptoms may be present shortly after starting cyclosporine and include seizures, encephalopathy, extrapyramidal syndrome, or posterior leukoencephalopathy (Ishikura, K., 2006). The latter, described first in 1996, consists of a reversible syndrome of headaches, altered mental status, seizures, and cortical blindness accompanied by multifocal bilateral white matter abnormalities seen on brain magnetic resonance imaging (Azzi JR, 2013).

Tacrolimus is associated with similar neurotoxic adverse events. Tacrolimus is slightly more neurotoxic (Farouk SS, 2020), (Vincenti F, 1997) and may have ototoxicity (Faravelli I, 2021).

The symptoms of CsA- and tacrolimus-associated neurotoxicity may be reversed in most patients by substantially reducing the dosage of immunosuppressant or discontinuing these drugs. However, some patients have experienced permanent or even fatal neurological damage even after dose reduction or discontinuation (Bechstein WO, 2000).

CNI-associated multiple electrolyte derangements including hyperkalemia, hypomagnesemia, hypercalciuria, metabolic acidosis, and hyperuricemia may be challenging to manage for the clinician. Finally, CNI-associated neurotoxicity, tremor, and defects in hair growth can have a significant impact on the transplant recipient's quality of life (Farouk, 2020)

Four alternative approaches to full-dose CNI therapy have emerged: ***(1) CNI minimization***, which reduces the amount of the drug administered. This strategy may be undertaken from the time of transplant (de novo) or later post-transplant either elective (proactive) or rescue (reactive) (Sharif A, 2014); as a result of an adverse event such as nephrotoxicity or BK viral infection; (***2) CNI conversion***, which tapers CNI dosing at any time post-transplant until full replacement with IS alternative is achieved. This strategy may be undertaken at any time post-transplant (early or late conversion usually based on the time either before or after 6/12 month duration post-transplant respectively) and is commonly used as a result of an unacceptable CNI-related adverse event; till now the early conversion strategy giving the best outcomes in selected patients (Leas BF, 2016); ***(3) CNI withdrawal***, which slowly eliminates the amount of drug administered early or late post-transplant. It shows short-term optimistic outcomes, but long term studies are required; ***(4) CNI avoidance***, which avoids the use of CNI in favor of other immunosuppressive drugs from the outset, carrying Increased rejection risk.

Another approach to overcome CNI overexposure is by co-administration of Inhibitors of CYP3A (e.g., ketoconazole) to decrease the exposure to CNI metabolites, but more frequent monitoring because of risk for overdosing. This approach is cost saving, but only very few studies on it (Naesens, 2009).

## Conclusion

CNI-based regimens remain the gold standard of care in organ transplantation even after 50 years of FDA approval. The current challenge is how to reduce the toxicity of the current regimens while maintaining safe and effective immunosuppression that improves the graft function and avoid drug long term drawbacks.

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