A Comprehensive Review of Calcineurin Inhibitors Used for Immunosuppression in Cardiac Transplantation

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Contents

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Abstract

Calcineurin inhibitors (CNIs) have been the foundation of immunosuppression in solid organ transplantation since the 1980s. Cyclosporine A (CSA), the first in class, was identified as the metabolite of the soil fungus *Tolypocladium inflatum Gams* as part of a larger program of screening for naturally occurring fungal metabolites with biologic activity in the 1970s. Significant immunosuppressive effects were discovered and consequently CSA was trialed as an immunosuppressant in renal transplantation. This initial success led to its widespread study and adoption in solid organ transplantation. This novel agent yielded significant improvements in both 1 year and longer-term allograft and patient survival. Subsequently, a similar and more potent CNI, tacrolimus was developed. Today, it is the principal CNI used for prevention of allograft rejection. Like all other immunosuppressives, the benefits of CNIs are counterbalanced by side effects and complications resulting from drug toxicity. This chapter comprehensively reviews the clinical use of CNIs in cardiac transplantation.

Keywords

Calcineurin inhibitors · Complications of immunosuppression · Heart transplantation · Immunosuppression

1 History of Calcineurin Inhibitors

The introduction of cyclosporine as an approved medication to prevent transplant allograft rejection in 1980s, followed several years later by tacrolimus resulted in a new era of greater survival solid organ transplants with calcineurin inhibition. One-year heart transplant patient survival increased from around 60% to the mid 80% (Cheung and Menkis 1998; Cheng 2013). Both medications originate from the microbiome. Cyclosporine, the prototype, was a peptide isolated from the filamentous fungus *Tolypocladium inflatum* in Norway in the 1970s (Borel et al. 1994). Its immunosuppressant properties were discovered by J.F. Borel in 1976 and the FDA approved it for use for immunosuppression in solid organ transplantation in 1983. In 1987, tacrolimus was isolated as a macrolide antibiotic with immunosuppressive properties from the soil bacterium *Streptomyces tsukubaensis* by Tohru Kino in Japan (Hatanaka et al. 1988; Kino et al. 1987). It was approved for solid organ transplantation by the FDA in 1994. Since the late 1980s calcineurin based immunosuppression has been the standard for solid organ transplantation.

2 Mechanisms of Action

Despite differing microbiotic origins, cyclosporine and tacrolimus share similar mechanisms of action as calcineurin inhibitors. They both bind to immunophilins. Cyclosporine binds cyclophilins and tacrolimus (also known as FK-506) binds FK-binding proteins in the cytoplasm of cells (Matsuda and Koyasu 2000; Dumont et al. 1992). These immunophilins are present in almost all cells of the body, sparing the progenitor cells of the bone marrow, giving the medications a wide variety therapeutic and toxic potential. Once bound to their respective immunophilins, these complexes competitively bind to and inhibit the phosphatase calcineurin. Calcineurin inhibition results in reduced activity of the transcription factors, most significantly the nuclear factor of activated T cells (NF-AT), that are needed for cytokine gene transcription activation (Wuederrecht et al. 1993). Importantly, the transcription of interleukin-2 (IL-2) is impaired by calcineurin inhibition, resulting in suppression of both cell-mediated and antibody-mediated immune responses. Aside from the drug class nomenclature associated calcineurin inhibition, CNIs are also involved in the inhibition of the mitogen-activated protein kinase (MAPK) pathway responsible for T cell-mediated production of the proteins JNK and p38 (Matsuda and Koyasu 2003). JNK and p38 upregulate the transcription of IL-2 in the nucleus and thus IL-2 is inhibited by yet another different pathway (Clerk et al. 1999). It is also known that the cytokine TGF-B1, an inhibitor of IL-2 dependent T cell proliferation is increased in both cyclosporine and tacrolimus administration (Das and Levine 2008; Ahuja et al. 1995; Kwiek et al. 2008).

3 Medication Forms and Routes of Administration

There are several modes of administration available to choose from for calcineurin inhibition in solid organ transplantation that can be tailored to patient needs and preferences. Cyclosporine exists in oral, intravenous, and ophthalmic formulations. Tacrolimus exists in oral, intravenous, and topical formulations. There are both brand name and generic forms available for use. The ophthalmic formulation of cyclosporine and the topical formulation of tacrolimus are not for use in solid organ transplantation.

The oral formulation of cyclosporine is available in a nonmodified form that depends on bile for absorption (Sandimmune®) and also more commonly used microemulsion formulations that do not rely on bile salts for absorption and demonstrate increased area under the curve bioavailability (GENGRAF®, Neoral®). Both nonmodified and modified forms are available in capsule and liquid form. The oral formulation of tacrolimus is available in both immediate release and extended release formulations designed for once a day administration. While there are studies demonstrating the safety and efficacy of extending release tacrolimus (Astagraf XL® and Envarsus XR®) regimens in cardiac transplantation, FDA approval has not yet been granted for this indication (González-Vílchez et al. 2018). Tacrolimus also has a sublingual formulation that can be used when the enteric route needs to be

bypassed in the cases of both poor absorption and rapid metabolism (Pennington and Park 2015). In cases when an oral route cannot be used, the unmodified version of cyclosporine can be given as a continuous intravenous infusion. Tacrolimus also has a preparation for parenteral administration. It is important to recognize that when switching between routes of administration and formulations, dose conversions are generally not one to one. A table of the typical dose ranges used in cardiac transplantation is listed below.

Standard cardiac transplant calcineurin inhibitor dosing regimens

	Brand name	Oral capsule and liquid dosing	Sublingual dosing	Intravenous dosing
Cyclosporine				
Nonmodified, oil-based formulation	Sandimmune® (generics available)	4–8 mg/kg daily in two doses 12 h apart	N/A	1–2 mg/kg daily in two 2–6-h infusions or continuous infusion
Modified emulsion	Neoral® Gengraf® (generics available)	4–10 mg/kg daily in two doses 12 h apart	N/A	N/A
Tacrolimus				
Short-acting	Prograf® (generics available)	0.05–0.1 mg/kg daily in two doses 12 h apart	0.025–0.5 mg/kg daily in two doses 12 h apart	0.01–0.02 mg/kg daily in two doses or continuous infusion
Extended-release	Astagraf XL® Envarsus XR®	N/A	N/A	N/A

N/A indicates that the formulation is either not available or not applicable to cardiac transplantation

4 Pharmacodynamics and Therapeutic Drug Monitoring

While initial dosing of CNIs may be estimated based upon patient weight, these drugs are all dosed to maintain specified therapeutic drug levels. The various CNI formulations have different pharmacokinetic parameters and are not interchangeable. The doses of both cyclosporine and tacrolimus should be measured using a 12-h trough or a 24-h trough in the case of the extended release preparation of tacrolimus. This trough is noted as the concentration at time 0 or C0. There is a consensus that monitoring cyclosporine levels 2 h after administration (C2) can measure levels that better correlate with graft outcomes (Levy et al. 2002). However, the logistics of this in the outpatient setting makes this method less feasible. In general levels of both cyclosporine and tacrolimus are maintained highest immediately post-transplant and then decreased over time. The goal is to maintain the lowest levels possible to minimize side effects while preventing rejection. Target drug levels are often individualized for patients to account for varying toxicities, renal

dysfunction, rejection history, malignancies, and current infection status or risk of infections. In general there is a target cyclosporine trough of 275–375 ng/mL during the first six postoperative weeks, 200–350 ng/mL for weeks 6–12, and 150–300 ng/mL for months 3–6. Then a long-term maintenance goal of 150-250 ng/mL is targeted (Costanzo et al). For tacrolimus, the goal trough levels are typically 10–15 ng/mL in the first 3 months, with reduced target levels of 8–12 ng/mL in months 3–6, followed by a long-term maintenance goal of 5–10 ng/mL after 6 months (Costanzo et al. 2010).

5 Interpersonal and Intrapersonal Variations in Drug Metabolism

Individual patient differences exist in the amount of active medication per dosage and are accounted for by various factors. Differences in weight and body surface area can cause certain patients to require different doses. The generally low bioavailability of both cyclosporine and tacrolimus is related to poor gut absorption, degradation by enzymes in the GI tract, and first pass hepatic metabolism. Thus, malabsorptive conditions can prevent absorption which can affect levels of both drugs. In addition, there are genetic polymorphisms with some association to race that cause differences in the metabolism of calcineurin inhibitors. The amount of active medication after single dose has been noted to be less in Hispanic and African American subjects as compared to Caucasian subjects (Mancinelli et al. 2001). This variation has been traced to genetic polymorphisms in the CYP3A5 gene (Oetting et al. 2016). There are two alleles inherited from each parent that encode for each CYP450 enzyme. In addition, spontaneous mutations can occur. There are three different possibilities for inherited metabolism. If two wild type normal alleles are inherited, the individual will have a normal metabolism of the CNIs. If a wild type and a variant allele are inherited, the individual will have increased metabolism and will likely require a higher dosage of CNI to achieve therapeutic levels. If there are two variant alleles inherited, the individual may be an ultra-rapid metabolizer requiring even higher dosages of CNI or demonstrating an inability to maintain therapeutic CNI levels. These variations in metabolism can result in difficulties maintaining therapeutic CNI levels and make patient management challenging.

Some commonly available foods also affect levels of calcineurin inhibitors. For example, grapefruit contains furanocoumarins that are strong inhibitors of the cytochrome P-450 3A enzyme leading to decreased metabolism and increased and potentially toxic concentrations of cyclosporine and tacrolimus (Guo et al. 2000). Cyclosporine interacts with bile salts and thus a lipid rich meal can alter levels of the medication (Guan et al. 2011). As mentioned previously, both CNIs require absorption in the GI tract and thus medication preparations that coat the GI tract and prevention absorption can alter drug levels (Steeves et al. 1991). Another cause of intrapersonal variations in CNI metabolism are other medications which may be accelerators or inhibitors via interactions with the hepatic cytochrome 3A4 pathway.

Cyclosporine and tacrolimus also bind to the transporter, P-glycoprotein, making them susceptible to drug interaction from this pathway (Christians et al. 2005).

The effects of maternal ingestion of calcineurin inhibitors on the developing fetus and neonate also deserve consideration as women of childbearing age may become pregnant while taking calcineurin inhibitors that are needed for maintenance of a solid organ transplant. Due to the presence of the near ubiquitous immunophilins, both cyclosporine and tacrolimus cross the placenta and are transmitted in breast milk. Although long-term effects are not known, studies do show tolerability in gestation and a breast feeding (French et al. 2003).

6 Commonly Used Medications and Interactions with CNIs

The general management of post heart transplantation patients involves treating infections and utilizing infection prophylaxis. In addition, clinicians need to treat the cardiometabolic conditions associated with transplant and transplant immunosuppression. Below is a table of the effect on CNI levels in medications of drug classes that are commonly considered for use in transplant patients. In the treatment of conditions not included here, it is important in general to know if a new medication that is being introduced is an inducer or inhibitor of the cytochromeP450 3A4 system (CYP3A4) or the P-glycoprotein (P-gp) systems. In addition to the table below, it is important to note instances in which cyclosporine and tacrolimus levels may not be specifically affected but the newly introduced medications are more toxic or less effective as in the case of statins and diabetic medications.

Agents affecting CNI levels in medication classes commonly used post cardiac transplantation

Medication class	Mechanism	Cyclosporine levels	Tacrolimus levels
Antifungals			
Azoles Caspofungin	CYP3A4 and P-gp inhibition Unknown	↑ ↑	↑ ↑
Antibiotics			
Nafcillin Macrolides Metronidazole	CYP3A4 competition CYP3A4 inhibition CYP3A4 inhibition	↓ ↑ ↑	↓ ↑ ↑
Antihypertensives			
Diltiazem, verapamil	CYP3A4 inhibition	↑	↑

↑ indicates and increase in the CNI level and ↓indicates a decrease in levels

7 Side Effects and Complications of Calcineurin Inhibitor Use

The side effects and complications relate to the fact that the calcineurin inhibitors bind to cytoplasmic proteins that are present in most cells, excluding the bone marrow. While patients are spared the myelosuppressive effects seen in azathioprine, multisystem effects can be seen and need close monitoring. Infectious and malignancy complications throughout the body are unintended consequences of alternations of the body's immune defenses and should be screened for with use of all immunosuppressants, including calcineurin inhibitors. For the purposes of this book chapter and in clinical practice it is useful to categorize side effects by body systems. A review of systems can capture the side effects of these medications and concerns picked up during a review of symptoms can be addressed to potentially improve quality of life in transplanted patients.

8 Renal

Renal dysfunction is a particularly concerning complication of calcineurin inhibitor therapy. There is a risk of acute nephrotoxicity during initiation of CNIs in the postoperative period. This acute toxicity tends to be reversible. However, the chronic irreversible kidney disease that can develop as a result of long-term CNI use is considered a major downside. The negative effect on renal function is multifactorial and known to be related to damage to the renal arteries and arterioles, glomerulosclerosis, tubular atrophy, and interstitial fibrosis (Puschett et al. 1990). Generally, the clinical toxicity is based on a clinical assessment. However, a renal biopsy is the gold standard test to diagnose calcineurin-inhibitor-induced nephrotoxicity. Acute toxicity is characterized by necrosis and early hyalinosis of smooth muscle cells in the afferent arterioles, and isometric vacuolization of the proximal straight tubules. In chronic toxicity, medial smooth muscle cells in afferent arterioles are replaced by beaded hyaline deposits that bulge into the adventitia. There is also interstitial fibrosis and tubular atrophy (Liptak and Ivanyi 2006).

9 Cardiovascular

CNIs alter the vascular system via several different pathways. One that is most easily picked up clinically is the development of hypertension. CNIs induce hypertension by increasing sympathetic nerve activity, augmenting vascular tone, and altering kidney sodium transport (Hoorn et al. 2012). Long-term survival of the allograft places patients at risk for long-term consequences to the vasculature, notably cardiac allograft vasculopathy. Cardiac allograft vasculopathy differs from nontransplant related coronary disease in that it tends to be caused by accelerated intimal hyperplasia resulting in diffuse disease rather than focal stenosis or plaque rupture events. It is often a pernicious condition, especially in heart transplant patients who have denervation that prevents the sensation of chest pain. However, it is associated with

significant mortality. A review of the UNOS database found that around 6% of patients with CAV experience sudden cardiac death (Vakil et al. 2014). CNIs are not associated with the progression of cardiac allograft vasculopathy but they do not prevent progression like mTor inhibitors, and this may factor into decision making regarding their use.

10 Neurologic

Some general neurological toxicities associated with CNI use involve mental status changes, seizures, headaches, paresthesias, and most commonly tremor (Coe et al. 2020). Neuropathy is more frequent in a CNI immunosuppressive regimen as compared to a CNI free regimen and patient symptoms improve with withdrawal of CNI. This was found to be related to increases in nerve excitability parameters, suggestive of changes in nerve membrane depolarization (Arnold et al. 2013). A rare but important complication to be aware of is reversible posterior leukoencephalopathy syndrome (RPLS). It is also known as posterior reversible encephalopathy syndrome (PRES). This is a diagnosis that requires both clinical and radiographic findings. Clinical symptoms are hypertension in combination with headache, altered mental status, seizures, and visual disturbances. Neuroimaging will show posterior-predominant vasogenic edema best captured by MRI because of the posterior location. RPLS can occur at any time. It is most likely to occur shortly after the initiation of CNI and is associated with supratherapeutic levels (Anghel et al. 2013). Risk factors for the development of calcineurin inhibitors-related neurotoxicity are conditions that affect myelin or alter the blood brain barrier such as the use of methylprednisolone, infections, arterial hypertension, fluid overload, and hypocholesterolemia (Senzolo et al. 2009). Screening for neurologic complications is an important part of post-transplant management and special consideration should be given to transplant recipients with preexisting neurologic conditions.

11 Endocrine and Metabolic

The CNI carries a risk for the development of diabetes mellitus which is more pronounced in patients that are taking tacrolimus in comparison with cyclosporine (Heisel et al. 2004). The new onset diabetes after transplant (NOAT) is multifactorial in origin. It is a result of both reduced insulin sensitivity and reduced insulin secretion by pancreatic cells (Chakkera and Mandarino 2013). There are also alterations in bone metabolism turnover seen with CNI, especially with cyclosporine that can contribute to the development of osteoporosis (Thiébaud et al. 1996). These effects are attenuated by concomitant steroid use. Alterations in lipid metabolism occur with calcineurin use that contributes to cardiovascular disease mentioned prior. CNIs, most commonly cyclosporine, can interfere with renal tubular excretion of uric acid and cause gout in some patients (Brigham et al. 2020).

12 Gastrointestinal

Some common side effects of the CNIs are nonspecific nausea, vomiting, diarrhea. At high levels, both cyclosporine and tacrolimus can cause cholestasis (Oto et al. 2010). However, tacrolimus has better GI handling producing superior outcomes in graft function in liver transplantation (McAlister et al. 2006). The gastrointestinal system may also be a site for post-transplant lymphoproliferative disorder that is related to increase immunosuppresion (Stojanova et al. 2011).

13 Integumentary

Skin cancers are the most common type of malignancy in transplant recipients on immunosuppression with calcineurin inhibitors with squamous cell carcinoma being the most common type (Euvrard et al. 2003). It is believed that cancer is triggered by the production of TGF-B1 associated with CNI use and IL-2 levels are lower in patients with post-transplant skin cancers (Imko-Walczuk et al. 2016). Patients should be advised to avoid sun exposure, wear sunscreen, perform self-administered skin checks and have regular expert dermatologic evaluations. Gingival hyperplasia, especially in the presence of nifedipine, can occur with cyclosporine use (Dongari et al. 1993). Hair tends to be affected differently depending on the calcineurin inhibitor chosen. Hirsutism is more common with cyclosporine while alopecia is a more common finding associated with the use of tacrolimus (Yamamoto and Kato 1994).

14 Calcineurin Minimization

A goal in post-transplant therapy is to use the lowest effective dose to preserve graft function. This is the role of frequent laboratory monitoring of immunosuppressant drug levels to ensure patients are in a therapeutic window while avoiding supratherapeutic values more associated with toxicity. Aside from monitoring to ensure that levels are in a therapeutic range and using the lowest effective dose, there are strategies of CNI minimization. An early transplant strategy for CNI minimization is the delay of the initiation of CNI immediately post-transplant. This is facilitated using immunosuppression induction agents. Basiliximab and thymoglobulin are the most commonly used induction agents for this purpose and are associated with less renal dysfunction in the immediate postoperative period (Rosenberg et al. 2005; Cantarovich et al. 2004; Ekberg et al. 2009). Another strategy for CNI minimization involves the use of other immunosuppressive agents with differing mechanisms of action that allow for reduced CNI dosing and in some cases complete CNI withdrawal. Steroids, mycophenolate mofetil, and notably mTOR inhibitors have been utilized for this strategy.

15 Conclusion

The advances in heart transplantation along with concomitant immunosuppression, of which calcineurin inhibition has a major role, have provided a mechanism of increased survival in people with advanced heart failure. Special attention to CNI related drug interactions and CNI toxicity both acutely and chronically is important to assure successful management of the organ transplant recipient. The role of clinicians taking care of post-transplant patients on calcineurin inhibitors involves close drug monitoring, assessment for the known possible multisystemic effects, and adjustments as needed to obtain an appropriate balance between mitigating side effects and obtaining graft saving immunosuppression.

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