Pathophysiology and treatment of calcineurin inhibitor nephrotoxicity

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Cyclosporine and tacrolimus are immunosuppressive agents used for prophylaxis against graft rejection in transplantation, and are often used off label due to their inhibition of T cell activation in autoimmune disorders.\textsuperscript{1} With the introduction of cyclosporine in the 1970s, transplant medicine was transformed. In 1984, tacrolimus was discovered and shown to be effective in human liver, kidney, and heart transplant recipients. In addition, tacrolimus did not have the adverse effects of hypertrichosis and gingival hyperplasia, and was associated with lower graft failure rates in kidney transplant patients when compared to cyclosporine.\textsuperscript{2,3} However, both cyclosporine and tacrolimus are limited by their nephrotoxicity. Cyclosporine has more data associated with its nephrotoxicity due to an extended time on the market. The nephrotoxic effects of tacrolimus may be slightly less, but ultimately the effects of both medications are thought to be due to a similar mechanism despite their structural differences.\textsuperscript{2,3} The rate of nephrotoxicity cited in the literature is variable (table 1), but is dependent on transplanted organ and years of exposure. For instance, 7-21\% of non-renal solid organ transplant recipients after five years of exposure to calcineurin inhibitors had chronic kidney disease (defined as a GFR <29ml/min/1.73M).\textsuperscript{4} In a study of 120 kidney-pancreas transplant recipients, after 10 years of calcineurin inhibition nephrotoxicity was universal on biopsy with 60\% of these patients having severe allograft dysfunction.\textsuperscript{5} While cyclosporine and tacrolimus are not structurally related, both agents work by inhibiting calcineurin, a calcium/calmodulin dependent phosphatase, which ultimately inhibits T-Cell activation. Cyclosporine binds to cyclophylin and tacrolimus binds with FKBP12. These complexes antagonize calcineurin preventing downstream phosphatase activity, including a decreased actuation of the nuclear factor of activated T- cells (NFAT). NFAT promotes transcription of IL-2 and activation of T-cells.\textsuperscript{2,6} Due to differences in molecular structure and binding characteristics, nephrotoxicity induced by cyclosporine and tacrolimus is thought to be related to the inhibition of calcineurin and NFAT.\textsuperscript{2,6} Initial consideration of cyclosporine-induced toxicity was thought to be a reversible side effect due to functional changes. This was known as acute nephrotoxicity.\textsuperscript{2} Unfortunately in 1984, Myers and colleagues suggested in heart transplant patients that long term use was associated with permanent and progressive tubule interstitial injury and glomerulosclerosis.\textsuperscript{7} The probable pathophysiology of acute and chronic injury due to calcineurin inhibitors (CNIs) will be reviewed (figure 1). **Acute CNI Nephrotoxicity:** Acute calcineurin inhibitor induced nephrotoxicity is primarily due to acute arteriolopathy. The original finding of acute arteriole vasoconstriction caused by cyclosporine on the afferent arterioles was first discovered by Murray and colleagues and later confirmed by subsequent studies.\textsuperscript{2} Additional research has shown a change in vascular flow and a decreased diameter of the afferent arteriole with cyclosporine treatment.\textsuperscript{8,9} Afferent arteriole vasoconstriction has been seen with tacrolimus but has a lower potential of acute arteriolar constriction compared with cyclosporine. This finding has been consistent in both animal and human studies.\textsuperscript{2,10} Even though tacrolimus has been found to have less arteriole vasoconstriction, it is still clinically significant and presents a significant challenge when managing patients.
The true etiology of acute arterial effects has yet to be clearly established. It is thought to be multifactorial, resulting from a combination of an increase in vasoconstrictive factors (endothelin and thromboxane), activation of the renin-angiotensin-aldosterone system (RAAS), reduction of vasodilator factors (nitric oxide (NO) and prostacycline), and formation of free radicals. Endothelin is released from cultured renal epithelial cells when exposed to cyclosporine. This finding has been confirmed in both animal and human studies with tacrolimus and cyclosporine. Additional endothelial dysfunction occurs via the inhibition of NO synthesis resulting in a decreased production of vasodilators. Endothelial dysfunction promotes platelet aggregation and prothrombotic activity in the glomeruli. Activation of RAAS system with CNIs involves both direct and indirect mechanisms. Directly, CNIs can activate juxtaglomerular cells to release renin. Indirectly, CNIs can cause renin release from decreased perfusion as a result of arteriolar vasoconstriction. Ultimately, increased renin production increases angiotensin II resulting in vasoconstriction. Additionally, decreased levels of cyclooxygenase (COX-2) have been found with CNI administration. This is due to an association with NFAT, which has important implications on the gene transcription of COX-2. By inhibiting calcinurein/NFAT, the production of COX-2 is attenuated which would contribute to afferent arteriole vasoconstriction. In addition to this arteriolar imbalance tacrolimus has been shown to activate the thiazide channel causing hypertension which directly contributes to long-term kidney damage.

**Chronic CNI Nephrotoxicity:**

Even though CNIs have significantly contributed to the advancement in transplantation, the disadvantage associated with CNIs is the chronic nephrotoxicity. This includes irreversible deterioration of renal function as a result of interstitial fibrosis, tubular atrophy, arteriolar hyalinosis, as well as glomerulosclerosis. Part of the mechanism of chronic interstitial nephritis is thought to be influenced by the acute effects. These include afferent arteriole vasoconstriction, local hypoxia or ischemia, free radical formation, and activation of the RAAS system, in particular angiotensin II and aldosterone.

Secondary release of aldosterone is thought to play a significant role in chronic CNI nephropathy. Aldosterone can release growth factors, release reactive oxidative species, and inhibit extracellular matrix degradation. Aldosterone inhibitors (eplerenone and spironolactone) have been studied for their protective effects in rodents. Rodents who received a mineralocorticoid receptor antagonist in addition to cyclosporine, compared to those who were just given cyclosporine, had significantly less associated arteriolar pathy and tubulointerstitial fibrosis, reduced renal tissue injury, hypofiltration, hypertension, and growth impairment. The rodents also sustained creatinine clearance. Sustained creatinine clearance suggests that inhibiting aldosterone may protect against acute nephropathy. Unfortunately, this has not been studied in humans.

Up regulation of transforming growth factor beta (TGF-F), a growth factor is also thought to have important implications in chronic CNI toxicity. TGF-F decreases the breakdown and encourages the production of extracellular matrix proteins, which ultimately promotes interstitial fibrosis. This growth factor has been shown to be elevated upon CNI administration. Other potential factors linked with CNI chronic nephropathy include macrophage infiltration, ischemia, and reactive oxidative species.
Prevention and Treatment of Nephropathy:
Managing the adverse effects associated with CNI toxicity can be challenging. Systemic hypertension is the primary adverse effect associated with renal artery constriction and activation of RAAS. Electrolyte disturbances can also result from CNI induced nephrotubular dysfunction resulting in hyperkalemia, hypomagnesemia, hyperchloremic metabolic acidosis, and hyperuricemia.²

A concentration toxicity relationship has been established with CNIs thus concentration dependent effects must be monitored. CNIs have a narrow therapeutic index in which high plasma concentrations can result in acute nephrotoxicity (leading to chronic toxicity), and low plasma levels are associated with graft rejection.¹⁷ Due to the high interpatient pharmacokinetic variability, particularly with absorption and metabolism, plasma concentrations should be measured to ensure the patient is optimally treated.¹,²,¹⁰ Unfortunately even with therapeutic drug monitoring, local renal accumulation can occur.²,⁸ Research has been done in transplant recipients regarding avoidance, withdrawal, and minimization of CNIs to prevent these toxicities. Current practice and research suggests minimization of CNIs after the initial transplant period to target lower plasma concentrations appears to be safe. However, there are no studies available to date that provide evidence supporting a reduction in CNI nephrotoxicity without an increased rejection occurrence.¹⁸

Because vasoconstriction of the afferent arteriole plays a central role with acute nephrotoxicity, medications that dilate the afferent arteriole have been studied to treat the acute toxicity. Treatment with a calcium channel blocker (CCB), such as amlodipine or nifedipine, has shown to improve blood pressure control and maintain glomerular filtration.² In renal transplant patients, use of a calcium channel blocker has additionally shown to have better renal allograft function independent of its effects on blood pressure after one year of therapy.¹⁶ In a Cochrane review of renal transplant patients, when compared to placebo, the use of a CCB resulted in a reduction of graft loss and improved glomerular filtration.¹⁷ In heart transplant recipients, CCBs helped improve both renal function and blood pressure. However, with long term treatment, CCBs did not influence the evolution of renal function.²,¹⁶,¹⁷ This study did not specify which type of calcium channel blocker, dihydropyridine vs non-dihydropyridine, was used. Different CCBs can affect renal vasculature and CNI metabolism differently.¹⁸

The central role of RAAS activation could suggest a role for an ACE inhibitor (ACEi) or angiotensin II receptor blocker (ARB). In rodents, it has been demonstrated that these agents can prevent cyclosporine induced interstitial fibrosis and improve renal function. In humans, ACEi have decreased CNI induced nephrotoxicity and improved alterations in blood pressure. ARBs have shown to decrease the plasma levels of TGF-B and endothelin. However, creatinine clearance tends to lack improvement due to decrease filtration as a result of dilation of the efferent arteriole.²,⁸,¹¹ As mentioned previously, spironolactone has shown in rodents to decrease aldosterone mediated effects, but no human studies are available.¹¹

There have been two randomized studies comparing lisinopril (an ACEi) versus nifedipine (a CCB) in renal transplant patients. Mourad and colleagues found no change in renal function and a similar change in mean arterial pressure.²⁰ Midtvedt and colleagues found that both lisinopril and nifedipine were effective in treating hypertension.²¹ However, patients receiving nifedipine had improved kidney
filtration rates and thus kidney function that was sustained over a period of 2 years.\textsuperscript{21} A Cochrane Review when comparing an ACEi with a CCB found a decreased GFR in humans and increased hyperkalemia with an ACEi. The incidence of decreased graft function was inconclusive. The only beneficial effect found was decreased proteinuria with ACEi use.\textsuperscript{19} Alternative agents have been studied for the treatment of chronic CNI nephrotoxicity including: misoprostol, L-arginine, anti-TGF-B antibodies, antioxidants, statins, and magnesium supplementation. These agents are lacking in human data, or have not shown a beneficial effect on chronic CNI toxicity in humans.\textsuperscript{2,8,11}

Tacrolimus and cyclosporine have become a cornerstone of transplant immunosuppression therapy. The agents differ in terms of molecular structure and side effects. Tacrolimus has more associated diabetes, tremor, and hypomagnesemia, while cyclosporine has the adverse effects of hirsutism, gingival hyperplasia, and higher low density lipoprotein (LDL) and triglyceride levels. However, both agents cause acute and chronic nephrotoxicity partially elucidated by the calcineurin inhibition. Both of these agents necessitate therapeutic drug monitoring to help limit these toxicities. Calcium channel blocking agents should be utilized for the treatment of hypertension and prevention of nephrotoxicity. Another important aim of therapy includes avoiding concurrent nephrotoxic medications. Future therapies focus on targeting other potential mechanistic causes of acute and chronic nephrotoxicity.

Figure 1: Calcineurin Inhibitor Nephrotoxicity

<table>
<thead>
<tr>
<th>Acute Nephrotoxicity</th>
<th>Chronic Nephrotoxicity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tubulo- Interstitial Electrolyte Disturbances</td>
<td>Interstitial Fibrosis &amp; Ischemia</td>
</tr>
<tr>
<td>↑ PLT Aggregation</td>
<td>↑ Prothrombotic Activity</td>
</tr>
<tr>
<td>↓ Vasodilators (Prostacycline &amp; NO)</td>
<td>↑ Vasoconstrictors (Thromboxane &amp; COX-2)</td>
</tr>
<tr>
<td>↑ COX-2 ↑ RAAS</td>
<td></td>
</tr>
</tbody>
</table>

PLT: platelet, NO: nitric oxide, GFR: glomerular filtration rate; RAAS: Renin-Angiotensin-Aldosterone System; ROS: reactive oxygen species, TGF-B: transforming growth factor beta
Table 1. Calcineurin Inhibitor

<table>
<thead>
<tr>
<th>Organ Transplant</th>
<th>Duration of Exposure</th>
<th>Calcineurin Nephrotoxicity (defined as decreased kidney function/histology)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kidney-Pancreas</td>
<td>1yr</td>
<td>30%</td>
</tr>
<tr>
<td></td>
<td>5yrs</td>
<td>55%</td>
</tr>
<tr>
<td></td>
<td>10yrs</td>
<td>100%</td>
</tr>
<tr>
<td>Orthotopic Liver</td>
<td>4yrs</td>
<td>16%</td>
</tr>
<tr>
<td></td>
<td>5yrs</td>
<td>18%</td>
</tr>
<tr>
<td>Bone Marrow Transplant</td>
<td>8yrs</td>
<td>67%</td>
</tr>
<tr>
<td>Pancreas</td>
<td>Induction at time of transplant</td>
<td>13%</td>
</tr>
<tr>
<td>*Autoimmune Uveitis</td>
<td>2yrs</td>
<td>21%</td>
</tr>
<tr>
<td>Heart</td>
<td>5yrs</td>
<td>9% ESRD</td>
</tr>
<tr>
<td></td>
<td>10yrs</td>
<td>9% ESRD</td>
</tr>
<tr>
<td>Lung</td>
<td>5yrs</td>
<td>14%</td>
</tr>
<tr>
<td>Intestine</td>
<td>5yrs</td>
<td>21%</td>
</tr>
</tbody>
</table>

References: