

Management of Calcineurin Inhibitors-Related Chronic Kidney Disease in Cardiac Transplantation

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Abstract

Background: The use of calcineurin inhibitors revolutionized transplantation by prolonging patients' survival. However, their utility is limited by the development of significant chronic kidney disease.

Methods: We reviewed the English literature looking for recent publications regarding the management of chronic kidney disease in cardiac transplant patients. We chose relevant papers based on design, number of patients and clinical utility.

Results: Most publications on the subject involve small populations with few prospective, randomized studies. Early use of tacrolimus appears to be associated with better kidney function after one year compared to cyclosporine. Once chronic kidney disease is established, successful strategies include reduction or elimination of calcineurin inhibitors while relying on mycophenolate mofetil, proliferation signal inhibitors or anti-CD 25 antibodies to prevent rejection. There is no follow up longer than two years with these approaches. Kidney transplantation might offer improved long-term survival compared to dialysis in end-stage disease.

Conclusions: Prospective studies with long-term follow-up are needed to decide about the timing and to confirm the utility of replacing calcineurin inhibitors with other agents in cardiac transplant patients with chronic kidney disease.

Introduction

The incidence of Chronic Kidney Disease (CKD) in Orthotopic Heart Transplantation (OHT) varies based on the definition used. In one large registry, CKD was defined as a Glomerular Filtration Rate (GFR) of less than 30 ml/min per 1.73m² of body surface area or the presence of end-stage renal disease (ESRD) [1]. The authors found a CKD incidence of 11 % at 5 years. In 2,709 Canadian OHT patients, dialysis was reported in 3.9% [2]. The occurrence of CKD after OHT is mostly related to baseline GFR, perioperative kidney injury and chronic toxicity from Calcineurin Inhibitors (CNIs) [1,3-5]. Patients' survival after developing significant CKD is decreased [1,2]. The use of CNIs leads to a biphasic change in renal function with an initial steep decline for the first 2 years followed by a slower change over several years [5-7]. This occurs despite reduction in CNI doses and levels late after OHT. During this slow progression phase, histologic damage continues unabated but is clinically under-appreciated [6,8]. CNIs cause acute afferent and efferent glomerular arteriolar vasoconstriction [9]. This continues to be seen chronically [6,10]. Histologically, there is hyalinosis impinging on the arteriolar lumen with myocyte necrosis and patchy ischemic damage downstream from the narrowed or occluded arteriole. The glomerulus is small and collapsed. There is tubular atrophy with interstitial fibrosis [6]. Nankivell et al. showed a histologic pattern of CNI toxicity that predominated after the first year and became universal at 10 years [8]. Tubulo-interstitial and glomerular damage, once established, was cumulative and irreversible [8]. CKD due to CNI toxicity most frequently presents with Hypertension (HTN), bland urine sediment with few cellular elements and non-nephrotic proteinuria [6,11].

Management

We will discuss two issues most often addressed by transplantation cardiologists; the management of hypertension and immunosuppressive drugs. Referral for nephrology consultation should be considered.

Treatment of HTN

Controlling HTN is important in any patient with CKD to slow disease progression [12]. This probably applies to OHT patients, although there is a dearth of data [13]. Multiple agents are frequently needed [14]. It is known that the frequency of HTN is higher with Cyclosporine (CSA) compared to Tacrolimus (TAC) [15]. However, TAC cannot be recommended solely on this basis as it could double the risk of new onset diabetes itself a risk factor for CKD. Many agents have been studied in animal models but few have been assessed in patients [15].

Calcium Channel Blockers (CCBs): CNIs cause vasoconstriction as noted above. CCBs, specifically vasodilating dihydropyridines, have been shown to improve renal plasma flow and GFR [9,16]. A small prospective study comparing amlodipine to placebo showed a slower decline in GFR at one year [13]. There was no effect on LV mass and only a modest decrease in proteinuria. Diltiazem did not appear to offer the same protection [14].

RAAS Inhibitors: The use of RAAS inhibitors is beneficial in most patients with CKD; however, this has not been shown in OHT patients. A systematic review of randomized studies in CSA-treated kidney

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transplant patients show, after a median of 27 months, a reduction in GFR (around 5.8 cc/min) with a reduction of proteinuria (decrease of 470 mg/day) [17]. It is uncertain if the reduction in proteinuria would translate into better outcomes in the long run. In fact, Opelz et al. showed, in a retrospective study of 1,744 OHT patients, that the use of RAAS inhibitors did not improve patient survival after 6 years [18]. The same study looked at 17,209 kidney transplant patients and showed no difference in graft or patient survival [18]. The use of spironolactone in rat models prevented the decline in GFR and the histologic changes seen with CSA [19]. There are no data in patients.

Modification of immunosuppressive drugs

Transplant centers have tried multiple immunosuppressive strategies in OHT patient with CKD to prevent progression of renal dysfunction. Most of the data come from small studies, limiting the strength of recommendations that can be made. Larger studies come usually from kidney transplantation literature.

Tacrolimus: In small studies, Tacrolimus (TAC) does not cause as much renal hemodynamic dysfunction as CSA [20]. Both appear to cause increased oxidative stress and TGF-beta production which appears to be responsible for the reported fibrotic changes [21]. In de novo OHT patients, a large study reported lower creatinine at one year on the combination of TAC/Mycophenolate Mofetil (MMF) compared to TAC/sirolimus (SRL) or CSA/MMF with creatinine levels of 1.3, 1.5 and 1.5 respectively. There was also less rejection with TAC/MMF versus CSA/MMF [22]. The kidney transplantation literature shows similar improvements in renal function when switching from CSA to TAC [23]. However, the renal literature points towards lower overall exposure to CNIs as the reason for improved creatinine [24]. CSA reduces MMF blood levels compared to TAC or placebo, so that switching off CSA allows the use of lower TAC doses without risking rejection [25].

CNI minimization and withdrawal: When CNIs are reduced or withdrawn, patients are usually switched from Azathioprine (AZA) to MMF or other immunosuppressants are added. Data are limited, mostly non-randomized and long-term follow-up is not yet available.

Mycophenolate Mofetil (MMF): Early small studies showed that switching OHT patients from AZA to MMF with a subsequent reduction in CSA could improve renal function [26-28]. Generally, shorter exposure to CNIs and greater reduction in CNIs' dose led to better outcomes. Also rejection and infection depended on the dose of MMF used to replace AZA. Patients' mortality was high, likely partially due to the degree of CKD. There were frequent gastrointestinal side effects limiting the dose of MMF.

In one large study, 2 sequential cohorts of de novo OHT patients were compared, the first one was treated with AZA and the second one with MMF (121 and 119 patients respectively) [29]. They targeted a lower CSA level on MMF (by 50 ng/ml) for the first 6 months. There was no difference in survival after 3 years (81% on MMF versus 78% on AZA). There was more grade 3A rejection on AZA despite higher levels of CSA and higher use of prednisone. There was no difference in the rate of infections. The calculated Creatinine Clearance (CrCl) was higher on MMF during the first 24 months of follow-up (72 ml/min versus 68 ml/min) but became insignificant at 3 years. Further reduction in CSA levels might be needed to sustain the early benefit.

The IMPROVED study enrolled prospectively 109 OHT patients with CKD (creatinine over 1.7 mg/dl) after a mean of 5.3 years post-OHT [30]. MMF was added to AZA in 89% of the patients and replaced

it in 11%. Prednisolone was continued or added at a dose of 7.5 mg/day in all MMF patients. CSA was reduced, after MMF level reached 2-4 mcg/ml, to a target trough level of 50 ng/ml. The control group comprised 52 patients who remained on AZA, nearly all of them were on steroids chronically. Thirty three of the 109 patients dropped out of the study prior or after CSA down-titration mostly due to gastrointestinal complaints. After an average of 8 months, creatinine decreased by more than 20% in 35% of MMF patients versus 4% of controls. Overall, creatinine decreased by 0.26 versus 0.08mg/dl. Only 3 episodes of easily treated grade 3A rejection occurred. Patients with DM benefited as well as those without DM. Only patients with a baseline creatinine over 3.5 mg/dl did not benefit. There were more infections in the MMF group.

In de novo OHT patients, the combination of TAC/MMF was as effective as TAC/SRL [22]. However, kidney function was worse on TAC/SRL. TAC/SRL was also associated with more fungal infections, impaired wound healing and interstitial pneumonia [22].

Proliferation Signal Inhibitors: PSIs have been advocated as replacement for CNIs or to reduce their dose. Their use without CNIs has been associated with increased Bronchiolitis Obliterans Organizing Pneumonia (BOOP) in some reports [31]. The combination has raised concerns of increased renal toxicity if the dose of the CNI dose is not reduced. They can worsen proteinuria [32-34]. Finally, they are associated with increased risk of mediastinitis and other infections [35].

Discontinuation of CNIs: This had been reported in several small studies. More recently, VENINAHTx, a randomized study enrolled 63 late OHT patients with CKD (GFR between 15 and 60 mL/min) [36]. CNI was stopped in 30 patients and was replaced with SRL. In the remaining patients, therapy was unchanged except for a reduction of 40% in the CNI dose. At one year, GFR improved only in the CNI withdrawal group (baseline to 12 months change of 36 to 55 ml/min versus 41 to 40 ml/min in the CNI dose reduction group). Six patients on low dose CNI (versus none off CNI) progressed to dialysis [36]. Lower baseline GFR did not predict poorer response as in other studies. Blood pressure was also reduced significantly off CNIs. There were more adverse drug related side-effects on SRL but this did not affect renal or graft outcomes. There were no significant differences in rejection episodes on routine biopsies at one and 3 months or coronary allograft vasculopathy on annual angiograms. The mean SRL trough level achieved was around 10ng/ml. The average SRL dose was 2 mg/day.

Raichlin et al. reported on a prospectively followed cohort of 58 OHT patients with CKD (GFR below 50 ml/min) who were taken off their CNI over a period of 3 months while SRL was introduced [37]. They were compared to 51 CNI treated control patients with CKD. The control group had been treated with a CNI for a longer period (mean 5.9 versus 4.6 years). After 2 years of follow-up, the GFR increased in the SRL group from 40.5 to 53.9 ml/min but decreased in the control group from 40.5 to 36.4ml/min [37]. GFR improved most in patients with the highest baseline GFR. Unfortunately, GFR worsened in 29% of SRL patients (decrease from 51 to 43ml/min). Also, proteinuria increased more in the SRL group (327 to 675 mg/day) versus controls (308 to 514 mg/day) at 2 years. However, this increase, which was very prominent after one year, slowed down at 2 years and the difference became statistically non-significant. There was an inverse relation between changes in GFR and proteinuria. Diabetic patients fared much worse with 40% of patients developing proteinuria greater than 1 g/day. ACE inhibitors prevented the increase in proteinuria. Ten percent of the patients stopped SRL due to side-effects [37].

Another study reported on 61 OHT patients, at least one year from the time of transplantation, who was switched from a CNI to SRL [34]. Forty-nine patients had CKD defined as creatinine over 1.7 mg/dl. Proteinuria was present in 31% of the patients at baseline and was high-grade (over 1 g/day) in 11.5%. At 24 months of follow up, 65% of the patients had an increase in proteinuria. The occurrence of high-grade proteinuria increased from 11.5 to 22.9% of patients at study end. There was an overall increase in GFR. A correlation was noted, however, between increased proteinuria and decreased GFR during follow up especially in the high-grade group (GFR decreased from 39.6 to 29.2 ml/min). Proteinuria was mitigated in patients treated with ACE inhibitors or angiotensin receptor blockers. Nearly 10% of patients with no or low level proteinuria at baseline developed high-grade proteinuria at follow-up [34]. It appears that discontinuation of the CNI might contribute to increased proteinuria [38].

Hunt et al. showed that, nearly one year after switching from a CNI to SRL, no patient with a creatinine below 2.5 mg/dl had progressed to ESRD, while four of 19 patients with a higher baseline creatinine required dialysis [39].

Reduction of CNIs dose: This was explored in several small retrospective studies with mixed results [38,40].

The VENINAHTx study, discussed above, is a prospective randomized study that showed improved renal function only in patients completely withdrawn from CNI therapy [36].

Gleissner et al, in a single center study, randomized 39 OHT patients with creatinine over 1.7 mg/dl despite 6 months of low dose CNI [41]. In 19 patients SRL was introduced and CSA was stopped. Therapy was not modified in the remaining patients. After 6 months follow-up, the SRL group had an increase in GFR from 48.5 to 61.7 ml/min while the group continued on low dose CSA had no change.

In another prospective pilot study, CADENCE, CNI dose was reduced after the introduction of everolimus. This led to continued decline in GFR after 12 and 48 weeks (68.9 versus 61.6 mL/min) [42,43].

The NOCTET study, a randomized, multicenter trial, enrolled 282 Thoracic transplant recipients with CKD who were at least one year post-transplantation. Most of them were followed for up to 2 years [44,45]. Everolimus (EVR) was added and the dose of CNI was reduced by close to 60%. The mean baseline measured GFR was close to 50 mL/min. There was a significant improvement of renal function at one and two years [44,45]. After 2 years, the measured GFR improved by 3.2 mL/min on EVR and decreased by 2.4 mL/min in controls. Shorter time from transplantation to enrollment was predictive of response, so that OHT patients enrolled more than 8 years after transplantation had no benefit from CNI reduction [44]. EVR was associated with twice as many pneumonias in the first year and 1.8 fold increases in risk of rejection after 2 years. Proteinuria was not reported.

To complicate the picture, the small, randomized SHIRAKISS study, showed that late addition of MMF or EVR while reducing CNI levels by 30% and 70% respectively, resulted in better renal function on MMF after 3 years [46,47]. This outcome was dependent on baseline proteinuria only with EVR. EVR-treated patients with baseline proteinuria below 150 mg/day did as well as MMF-treated patients.

Results in de novo and early OHT: The use of PSIs instead of CNIs appears problematic in de novo OHT especially in light of the discontinued Heart Spare the Nephron trial [48]. In this study, patients were switched from a CNI to SRL 12 weeks after OHT. Four out of 7 patients in the SRL arm had grade 3A rejection [48]. No rejections were

noted in the CNI arm. The combination of PSIs with CNIs in de novo OHT patients does not improve renal function even when a reduced dose CNI is used [22,32,35,49,50]. There is no change in survival. There is a significant increase in bacterial infections, including mediastinitis but less viral infections [35,49,50]. Increased diagnosis of new onset DM is reported [35,50,51]. Pericardial effusions are also more common [49,50].

Results in renal transplantation: Similar results have been seen in larger studies in kidney transplantation [52-54]. The CONVERT trial randomized 830 patients at least 6 months after kidney transplantation to CNI replacement with SRL [53,54]. It showed some benefit only in a subpopulation of patients with a GFR greater than 40 mL/min and minimal proteinuria at baseline (estimated GFR at 24 months of 63.8 versus 59 mL/min with continued CNI).

Conclusion: The above studies highlight the complexity involved in using PSIs in this context. These drugs are associated with many side effects leading to discontinuation [55]. Kidney function at the time of introduction of the drugs should be moderately decreased to see the most benefit and although patients with GFR below 30mL/min can benefit many of the above studies showed that more patients with poor baseline GFR will progress despite PSI therapy due to advanced, irreversible CNI kidney toxicity [56]. The presence of baseline proteinuria is cause for concern as is the presence of diabetes and might negate any benefit of PSI use [34,37,46,47,54]. The use of ACE inhibitors and angiotensin receptor blockers might mitigate the adverse effect of PSI induced proteinuria on worsening renal function but this is not based on large number of patients [34,37,57]. The above highlight the need for more studies regarding this evolving issue. If the patient is placed on a PSI, they should have baseline then serial measurements of proteinuria. ACE inhibitors should be considered. Monitoring for rejection is performed routinely and drug levels should be followed and maintained rigorously in the therapeutic range to minimize complications.

Antibodies: Anti-CD25 antibodies (basiliximab and daclizumab) have been used in de novo OHT patients to delay the initiation of CNI in patients at high risk for acute kidney injury [58,59]. In one study, delaying the start of CNIs by 4 days led to a lower rise in average creatinine level during hospitalization when compared to historical controls (change in creatinine was -0.1 versus + 0.5 mg/dl) [59]. Other small series used anti-thymocyte immunoglobulins to decrease the dose of CNI or delay their start in patients with or at risk for CKD [58,60]. There was evidence of renal protection.

Anti-CD25 antibodies have also been used later and for longer periods after OHT to improve CKD [61-63]. They were used every 3 to 8 weeks with discontinuation of CNIs. In some cases, CNIs were restarted once kidney function improved. Three patients were treated for few months and up to one and a half years.

Kidney transplantation: Because ESRD carries a high mortality risk in OHT patients, kidney transplantation has been considered. Ojo et al. reported on 3,297 solid-organ non-renal transplant patients with ESRD who received kidney transplants, including a third that had OHT [1]. He noted an increased early mortality risk after kidney transplantation compared to dialysis (Relative risk of 3.42). It took nearly 1.4 years before the benefit of kidney transplantation became obvious but it persisted for 5 years [1].

In a smaller cohort OHT patients that had kidney transplantation for ESRD had better survival than those who remained on dialysis [2]. After 5 years, those transplanted had a survival of 78.6% versus 15.7%

for those on dialysis. Similar findings were reported in two papers while a third one noted much lower survival after kidney transplantation [64-66]. Finally, concomitant kidney transplantation and OHT have been anecdotally performed [67].

Conclusion

Put together, the above studies show that interventions that improve CNI toxicity should be deployed early before kidney function deteriorates significantly, and that the reduction in CNI dose should be large to be beneficial. Discontinuation of CNIs appears to offer better protection against progression of CKD. Drug level monitoring is important to ensure low rates of rejection. MMF appears to be the safer approach, if tolerated, as it clearly has no renal side-effects. However, it might not be enough for many patients to allow complete discontinuation of CNIs. PSIs are promising but are associated with many side-effects including the potential for worsening renal function and increasing proteinuria. Whether the use of renin angiotensin system inhibitors would address this concern is an open question. Early after OHT, the risk of rejection is high off CNIs and the benefit of alternative therapies is less evident. Prospective, long-term studies are still needed despite significant progress made recently.

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