Editorial Review

Chronic allograft nephropathy—clinical guidance for early detection and early intervention strategies

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Introduction

Improvements in reducing acute rejection rates following kidney transplantation in the last decade have not been mirrored by improvements in long-term graft survival rates [1,2]. One of the major causes of late graft loss in renal transplant recipients is chronic allograft nephropathy (CAN) [3–5] (Figure 1). CAN is highly prevalent in renal transplant recipients, with moderate to severe CAN present in 24.7% of recipients at 1 year post-transplant and in 89.8% of recipients by 10 years post-transplant [6]. CAN is defined by the histopathological features of interstitial fibrosis and tubular atrophy, but can also be associated with subclinical rejection, transplant glomerulopathy [6–8] or transplant vasculopathy caused by smooth muscle cell proliferation [4,9]. Therefore, the term CAN is being employed quite widely to describe a clinical syndrome instead of defining the presence of interstitial fibrosis or tubular atrophy. In order to avoid misinterpretations of this term, at the most recent ‘Banff’ meeting, it was proposed that pathologists no longer use this term, and simply refer to interstitial fibrosis and tubular atrophy (IF/TA) [10]. The term ‘chronic rejection’ has also been suggested as a possible replacement for CAN. However, this implies the pathology has an immune aetiology. As a pathological change often precedes any deterioration in function, the alternative term ‘chronic allograft dysfunction’ also has limitations. The revised Banff classification now recognizes chronic antibody-mediated rejection, in addition to IF/TA, broadening the underlying pathological lesions and pathophysiology of patients with ‘CAN’. As this article was developed prior to publication of the Banff report, we have used the term ‘CAN’ throughout to describe the clinical syndrome, consisting of all the above histological changes and their associated decline in renal function, and not a specific disease with particular causality.

The onset of CAN occurs early post-transplant, with histological damage associated with CAN occurring before changes in renal function are observed [6,8,11,12]. The initial interstitial fibrosis that occurs within the first year post-transplant leads to irreversible glomerulosclerosis in the later stages of CAN [6,13,14]. It is this glomerulosclerosis that causes a decline in renal function (observed as decreased glomerular filtration rate [GFR] and increased serum creatinine) [6]. Indeed, by the time changes in serum creatinine are observed, histological changes are severe and probably cannot be reversed [8]. However, interstitial fibrosis and glomerulosclerosis may appear independently of each other and may result from other factors leading to histopathological changes following renal transplantation. Various hypotheses have been suggested concerning the link between interstitial fibrosis and glomerulosclerosis, and whether the fibrotic process negatively and progressively affects neighbouring nephrons, leading to renal damage [15]. Therefore, insights derived from animal models might be useful in elucidating the mechanisms of glomerulopathy after transplantation [16].

There are a number of both immunological and non-immunological risk factors for CAN [4,8]. The major immunological risk factors for CAN include acute rejection, subclinical rejection and antibody-mediated chronic rejection that damage the allograft and impair graft function [4,6,8,17,18]. The non-immunological risk factors for CAN include donor and recipient characteristics such as obesity, hypertension, hyperlipidaemia and diabetes. The choice of immunosuppressive agent may also have an impact on the development of CAN, and calcineurin inhibitors (CNIs) are a significant risk factor for CAN [6,8,19,20]. CNI nephrotoxicity causes arteriolar hyalinosis and striped fibrosis from 3 to 6 months post-transplant, although at this early...
Fig. 1. Causes of graft loss in Australia in 2005 [3]. Chronic allograft nephropathy is a major cause of graft loss. CAN, chronic allograft nephropathy.

stage it is often transient [6] and may potentially resolve with CNI dose reduction [19,21].

Early detection and intervention strategies are important in managing the risk of CAN before it develops in both de novo and maintenance renal transplant recipients [8,14,22]. Currently CAN is not being detected in time for changes in therapy designed to prevent graft loss [8,23]. Therefore, there is a need to increase awareness and understanding of the progression of CAN. This paper provides practical guidance in the role of early detection before CAN becomes established, and early therapeutic intervention strategies in managing CAN to reduce its burden on renal transplantation. There have been a number of approaches discussed for minimizing CAN including CNI minimization or elimination strategies incorporating the use of mycophenolate mofetil (MMF) [24–26], or proliferation signal inhibitors (PSIs)/mammalian target of rapamycin (mTOR) inhibitors [8]. The focus of this paper is on the potential role of PSIs in early intervention of CAN.

Clinical guidance—early detection before CAN becomes established

Early intervention of CAN should be a key focus for transplant nephrologists, and improving early detection of CAN may allow early intervention through changes in immunosuppressive therapy, thus stabilizing disease progression. Since CAN is defined through histology, the only true confirmation of disease is by biopsy [8,27–29]. Whilst clinical studies have demonstrated that protocol biopsies at 1 month, 3 months and 1 year post-transplant detect early signs of CAN [28], this technique is often not performed in clinical practice due to its invasive nature and, in some countries, through a lack of reimbursement costs. Although the histological diagnosis of CAN is a relatively safe and valuable method of detecting subclinical disease, considerations regarding the traditional approach of estimating chronic damage should be taken into account. Visual, semiquantitative assessments of IF/TA, vascular intimal fibrosis, and glomerulosclerosis using Banff scores are easy to apply, but lack high interobserver reproducibility, contributing to their variable predictive and diagnostic values [30,31]. Many clinicians therefore rely on observing changes in serum creatinine to identify patients with suspected CAN, and then perform a biopsy to confirm the findings. However, since changes in serum creatinine occur at a late stage in the progression of CAN, there is an increasing concern that this underestimates the severity of histological changes and may be too late for intervention strategies to be effective [8]. In support of this, clinical studies have reported that serum creatinine underestimates deterioration in GFR (Figure 2) [8,29] and is a poor predictor of both CAN and graft loss [32]. Deterioration of GFR occurs before changes occur in serum creatinine, and these changes in serum creatinine are only observed once GFR falls below ∼30 mL/min [8].

Evolution of renal function, observed through changes in estimated GFR (eGFR), is a better predictor of graft loss than serum creatinine, with an >10% decline of renal function at 3 months post-transplant being more predictive of graft loss than isolated serum creatinine measurements [33]. A deterioration in renal function of more than 10% at 3 months post-transplant is associated with a 2.5-times relative risk of 10-year graft loss and predicts ∼15% reduction in long-term graft survival [33]. This should prompt physicians to initiate early intervention. There have been a number of formulae developed to estimate GFR; these are generally reliable between 30 and 70 mL/min, where the predictive value of serum creatinine is poor [8]. Measured GFR (mGFR) is a more accurate measure of renal function than eGFR, since eGFR is based largely on variable serum creatinine levels and fixed or predictable parameters such as gender, race, height and age [34,35].

In the absence of the facilities or funding for protocol biopsies, and given the poor predictive value of serum creatinine, there is a need to increase awareness of early detection of CAN and approaches for an early intervention before CAN occurs. Measured GFR provides the most accurate analysis of renal function and, where possible, we recommend that it should be routinely monitored early after transplantation. There are a number of different techniques that can be used to measure GFR; of these, inulin clearance is the
historical gold standard but alternative substances such as iodine-labelled iothalamate, $^{51}$chromium ethylenediaminetetra-acetic acid and $^{99m}$technetium diethylene-triamine-penta-acetic acid have also been used to provide 4-h measurements of GFR through measurement of blood clearance rates [8]. These techniques require an experienced nuclear medicine department and time commitment from the patient. One alternative approach that is implemented for patient convenience is the evaluation of creatinine clearance measured by 24-h urine collection, which can be done at the patient’s residence [36]. Slope analysis can then be applied to analyse the change over time of creatinine clearance [37] and includes the assessment of early reduced graft function (intercept) and the subsequent rate of graft loss (slope). Slope analysis is determined from the reciprocal relationship between GFR and serum creatinine, plotted as 1/serum creatinine, or can be plotted from eGFR or mGFR values [38,39]. Slope analysis demonstrates that lower renal function results in a faster decline in renal function over time. The endogenous protease inhibitor, cystatin C, can also be used to measure renal function. Serum cystatin C is reportedly sensitive enough to detect mild GFR reduction between 60 and 90 mL/min/1.73 m$^2$ [40]. Studies analysing the accuracy of cystatin C for determining GFR report that it is possibly a better filtration marker for measuring renal function than creatinine clearance [35].

A number of studies have investigated alternative non-invasive techniques that measure vascular and urinary flow, including real-time contrast-enhanced sonography and Doppler imaging [41,42]. Early data suggest that these techniques may improve the early detection of CAN; however, it remains to be seen how widely they will be used in clinical practice. Doppler imaging has served as a prognostic tool for identifying patients at risk of CAN, based on predicting the outcome following angioplasty or surgery [43]. High renal resistance prior to revascularization was a strong predictor of worsening renal function and blood pressure despite surgical correction [43].

Clinical guidance—early intervention through identification of risk factors before CAN occurs

As previously discussed, early intervention of CAN, facilitated through improved early detection, may stabilize disease progression and reduce the burden on long-term graft failure. The approach to minimizing CAN should include both preventative and therapeutic measures and should target the main risk factors for CAN (e.g. standard-dose CNI and acute rejection episodes) (Figure 3) [4,8,21,44].

Current therapeutic strategies for patients with CAN involve the minimization or elimination of CNIs from immunosuppressive therapy, thus aiming to reduce the extent of CNI nephrotoxicity and arteriolar hyalinosis [8,21]. Newer immunosuppressive agents, such as the PSIs everolimus and sirolimus, allow a halving of CNI exposure, and may reduce nephrotoxicity and improve renal function [45,46]. Everolimus is currently licenced for use in combination with low-dose ciclosporin (CsA), and the effect of everolimus and CNI minimization or withdrawal for the intervention of CAN is currently being investigated in a number of global clinical trials. A small number of studies have examined the effect of sirolimus and CNI minimization on CAN. These studies have observed both a lower incidence of CAN [47] and attenuation of the progression of early-stage CAN [48,49]. The use of sirolimus in de novo renal transplant recipients has been evaluated in a number of studies, where CNIs were withdrawn ~3 months post-transplant. Long-term data from 2 years post-transplant suggest that this approach results in fewer histological lesions of CAN and improved renal function when compared with patients receiving continued CNI-based therapy despite a modest increase in acute rejection rates [46,50–54].

Sirolimus has also been examined in maintenance renal transplant recipients with established CAN. In this setting, conversion from CNIs to PSIs may be successful in reducing and can lead to an improvement in renal function [55–59], although this effect is not observed in all patients, especially those with more severe CAN, when irreversible histological damage is present [59]. In fact, multivariate analysis has shown proteinuria >800 mg/day to be an independent predictor for worse outcomes, leading to the proposal that patients with proteinuria >800 mg/day should not be converted from CNIs to PSIs [56], and conversion from CNIs to PSIs in patients with a baseline creatinine clearance of <40 mL/min has also been associated with poor renal function [60]. A recent report by Diekmann and Campistol discusses conversion protocols for maintenance renal transplant recipients with CAN, and could be referred to for practical guidance in this area [60].
Further to reducing the impact of CNI nephrotoxicity, therapeutic intervention for CAN must also address the other major risk factors. The number of acute rejection episodes has a direct impact on CAN [8]. Whilst CNI minimization or withdrawal may reduce the impact of CAN, it is essential that changes to immunosuppressive therapy maintain a low incidence of acute rejection. Following on from early studies utilizing everolimus and full-dose CNI, everolimus in combination with low-dose CNI has been shown to provide a low incidence of acute rejection in de novo renal transplant recipients whilst maintaining renal function [61,62]. However, the early withdrawal of CNIs from sirolimus-based regimens has been associated with an increased incidence of acute rejection in a meta-analysis of six trials [63], and is not advised in the first 3 months post-transplant [64]. Therefore, when using PSI-based therapies, CNI dose should be reduced once therapeutic blood levels of the PSI are achieved. However, if early withdrawal of CNIs is used, patients should be carefully monitored to avoid acute rejection episodes. For everolimus, trough blood levels of 3–8 ng/mL are adequate to maintain immunosuppressive efficacy and are usually achieved within 4–5 days. CNI dose should then be reduced allowing lower CNI blood levels to be achieved [65]. For sirolimus, trough blood levels of 8–12 ng/mL are adequate to maintain immunosuppressive efficacy and are usually achieved within 6–8 days.

Clinical trials have shown that there are some specific adverse events associated with the class actions of the PSIs. These include wound healing issues, proteinuria, dyslipidaemia and other haematological effects. Most adverse events are generally mild and can be easily managed by simple interventions. Potential wound healing complications can be minimized through meticulous surgical techniques, the use of nonabsorbable sutures and the delayed removal of skin clips [65]. It is recommended that proteinuria and hypertension be managed through use of angiotensin-converting enzyme (ACE) inhibitors and/or angiotensin receptor blockers (ARBs) [65]. Proteinuria can also be managed through maintenance of low PSI trough blood levels, or even through reintroduction of minimal doses of CNIs to partly reverse proteinuria. Management of dyslipidaemia should focus on lifestyle changes and treatment with statins. Use of erythropoietin may be necessary in cases of severe anaemia [65].

PSIs are not inherently nephrotoxic but a synergistic toxicity has been observed with the combination of sirolimus with CsA. Specifically, sirolimus has been shown to enhance CsA activity by increasing the brain concentration of CsA and enhancing the negative effects of CsA on mitochondrial metabolism in the rat brain tissue [66,67]. In contrast, everolimus had the opposite effect. Sirolimus has also been shown to significantly increase the nephrotoxic effects of CsA in a further rat model, compared with equivalent trough levels of everolimus and CsA [68].

To further reduce the impact of CNI nephrotoxicity on the development of CAN, CNI elimination from a mycophenolic acid (MPA)-based regimen has been evaluated in clinical trials. Withdrawal of CsA from an MMF-based regimen resulted in an increased risk of acute rejection episodes and graft loss over the 5-year study period [69]. Conversely, studies in patients with chronic allograft dysfunction or CAN have shown that CNI withdrawal from MMF therapy is associated with improved renal function and no increased incidence of acute rejection [70,76]. Thus, further research is needed before clear recommendations can be made.

The efficacy and safety of PSIs in combination with MPA agents has been evaluated in order to establish an alternative CNI-free regimen. Sirolimus, in combination with MMF, demonstrated comparable efficacy to a CsA and MMF regimen in renal transplant recipients [71]. Similarly, a CNI-free regimen using sirolimus and MMF was associated with similar rates of acute rejection, graft survival and renal function post-transplant compared to tacrolimus and MMF [72]. Furthermore, a randomized, prospective trial reported that, following 5 years of treatment, CNI-free
imunosuppression with sirolimus and MMF was also associated with fewer graft losses due to CAN and better renal function than a CsA and MMF regimen [73]. Results from an open-label study of an everolimus/enteric-coated mycophenolate sodium (EC-MPS) CNI-free regimen versus an EC-MPS/CsA-containing regimen in 300 de novo renal transplant recipients are expected in 2008 and eagerly anticipated.

In addition to changes in immunosuppressive therapy, risk factors for CAN such as hypertension and hyperlipidaemia should also be managed aggressively through the use of lipid- and blood pressure-lowering therapies. PSIs can be used with statins and anti-hypertensive therapies in renal transplant recipients and the antiproliferative effects of PSIs may be enhanced by a concomitant statin use [74,75]. PSIs have dual actions and both everolimus and sirolimus have antiproliferative actions that have been shown to prevent smooth muscle cell proliferation in preclinical and clinical studies [76–78]. Since smooth muscle cell proliferation is a key component of CAN [4,9], this antiproliferative activity may provide extra benefits and have a beneficial role in reducing CAN. In fact, data from animal studies suggest that PSIs, either alone or in combination with other immunosuppressants, may ameliorate CAN [78–82]. Strategies to help prevent CAN may be utilized in patients at maximum risk. Specific factors pertaining to the individual donor and recipient include reducing ischaemic injury, maximizing graft function and optimizing human leukocyte antigen (HLA) match. Increased surveillance in patients at high risk of developing CAN, such as those receiving organs from older donors, may also allow for early intervention.

Conclusions

Prevention and early intervention in CAN remain long-term unmet medical needs in renal transplantation, as CAN eventually affects the majority of CNI-treated renal transplant recipients. CAN is usually not being detected early enough for treatments to effectively stop progression and prevent graft loss. Therefore, in the absence of routine protocol biopsies in many transplant centres, there is a need to improve early detection of CAN through recognition of early clinical signs of renal damage such as changes in mGFR or eGFR, which alert physicians before changes in serum creatinine or proteinuria. In this way, early identification of risk factors before CAN occurs, along with earlier detection, may prompt early intervention, with clinicians making changes to immunosuppressive regimens that may improve the outcomes of CAN. The use of PSIs early post-transplant may aid the management of CAN through minimizing the use of CNIs, maintaining a low level of acute rejection and by reducing smooth muscle cell proliferation within the kidney. This approach is currently being investigated in a series of global clinical trials. In addition, a CNI-free regimen utilizing mycophenolate therapy alone, or in combination with a PSI, may result in an improvement in renal function and graft survival without increasing the risk of acute rejection in patients with CAN. Long-term data also demonstrate that, compared to a CNI and MPA based regimen, MPA and PSI combination therapy preserved renal function and resulted in fewer graft losses, further suggesting that this regimen is a viable therapeutic option in the management of CAN.

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