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Pathogenesis and Management of Chronic Allograft Nephropathy

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Abstract

Chronic allograft nephropathy (CAN) is a common cause of late kidney transplant failure, characterized by progressive histological damage in the allograft. Although functional biomarkers such as creatinine are typically used to predict CAN, recent evidence suggests that composite, quantitative histological indices may be better predictors of long-term graft outcomes. Calcineurin inhibitors (CNIs) have been associated with major improvements in early rejection outcomes, but appear to cause both acute and chronic nephrotoxicity. The acute phase is associated with functional nephrotoxicity and is reversible with a reduction in CNI dosage, whereas the chronic phase is characterized by persistent histological lesions that are typically irreversible. Results from recent clinical trials suggest that converting from a CNI to sirolimus, withdrawing a CNI from a sirolimus-based regimen or using a CNI-free strategy may improve long-term outcomes by reducing CNI-related nephrotoxicity. However, in the *de novo* transplant setting, triple therapy with sirolimus, mycophenolate mofetil and corticosteroids is not recommended in combination with basiliximab induction. A treatment algorithm, based on the patient's histological score obtained on an allograft biopsy taken at approximately 6–12 months post-transplant, has been developed by our group and is described here.

1. Chronic Allograft Nephropathy

With improved immunosuppressive therapies, chronic allograft nephropathy (CAN) has replaced early severe acute rejection as the main cause of kidney transplant failure. CAN is a multifactorial disease (associated with acute rejection, human leukocyte antigen [HLA] mismatching, donor-specific antibodies, inadequate immunosuppression, donor age, brain death, ischaemia/reperfusion injuries, hypertension, hyperlipidaemia, infection, calcineurin inhibitor [CNI]-related nephrotoxicity, etc.) and represents the cumulative response to injury, regardless of the aetiology.[1-4] CAN is a histological diagnosis characterized by interstitial fibrosis, tubular atrophy, vascular occlusive changes and glomerulosclerosis described by the early pioneers nearly 50 years ago.[5-7] It is typically graded using the Banff '97 working classification.[8] However, the term 'chronic allograft nephropathy' was eliminated from the Banff schema at the 8th Banff Conference in 2005 and was replaced with 'interstitial fibrosis and tubular atrophy not otherwise specified' (IF/TA NOS).[9]

Another grading system used to assess chronic allograft injury, the Chronic Allograft Damage Index (CADI), is also often used to quantify histological manifestations occurring in the allograft.[10,11]

Much of the recent advances in our understanding of CAN have come from long-term histological studies using data obtained from protocol-driven biopsies. One such study evaluated the natural history of CAN over a 10-year period in a prospective study of 120 kidney transplant patients.[12] The study showed that there are two discrete phases of CAN: an initial phase of tubulointerstitial damage within the first year after transplantation, and a second subsequent phase of microvascular and glomerular damage with progressive interstitial fibrosis and tubular atrophy. The initial phase was associated with ischaemic injury and acute and subclinical rejection, whereas the second phase was accompanied by an increasing prevalence of CNI nephrotoxicity. By 10 years post-transplantation, severe CAN was present in 58% of patients.

2. Surrogate Endpoints for Long-Term Graft Outcomes

Clinical studies have demonstrated that several clinical risk factors are associated with CAN. However, most investigations have focused on the validity of using a single biomarker (fibrosis, creatinine, glomerular filtration rate [GFR], etc.) as a surrogate for predicting CAN. In two of our recent studies,[13,14] the transplant patient could have more than one risk factor that in different severities was/were associated with different combinations of histopathological lesions. Given the complex relationship between clinical risk factors, early histopathological changes and graft outcome, we concluded that composite, quantitative histological indices are best suited to guiding renal transplant prognosis. Thus, we believe that combined (composite) histological scores rather than single lesions should be used for the assessment of organ status and prediction of longevity. In the Banff 1997 CAN grading (later called IF/TA NOS in 2005), only two parameters – interstitial fibrosis and tubular atrophy – were accepted as criteria in the grading of the overall intensity of chronic allograft injury, compared with six parameters contributing to CADI. Three recent studies have also found that other histopathological parameters such as inflammation and vascular intimal thickening, in addition to interstitial fibrosis and tubular atrophy, are morphological correlates of ongoing allograft damage and should be considered when grading CAN.[15-17] Thus, Banff '97 and Banff '05 CAN grading with its current components may underestimate the severity of disease and could lead to inappropriate assessment of the degree of CAN. In a recent study by our group,[14] we assessed the prognostic values of different composite scores: CADI (= i [interstitial mononuclear infiltration] + ci [chronic interstitial fibrosis] + ct [chronic tubular atrophy] + cv [chronic fibrointimal vascular thickening] + mm [mesangial matrix increase] + glomerular sclerosis), the sum of the Banff Chronic score (= ci + ct + cg [chronic glomerulopathy] + cv + mm) and grading (CAN; mild, moderate and severe) for predicting allograft dysfunction/graft loss using Cox proportional hazard modelling in 318 consecutive 6 months surveillance biopsies. CADI score outperformed the other variables in its ability to predict graft outcome.

Many centres are reluctant to perform surveillance biopsies, as this is an invasive procedure. As a result, many transplant centres appear to use early functional biomarkers as a replacement for histopathology. Several retrospective observational studies have demonstrated that serum creatinine[18-20] or GFR[21] is correlated with renal allograft survival. However, whereas correlation provides an indication that there is a relationship between two variables, it does not indicate that one variable causes the other. Thus, changes in the value of a good predictive marker should, with high sensitivity and specificity, predict changes in the endpoint of interest. Serum creatinine and estimated GFR (eGFR) have not been rigorously evaluated in this regard; nevertheless, they have been widely adopted as surrogate markers for CAN in many transplant centres. A recent study by Kaplan and colleagues[22] demonstrated that serum creatinine at 1 year was a poor predictor of allograft loss at 2 years (area under the

receiver operator characteristic curve [AUROC] = 0.63). These results illustrate the situation where a test result may have a good correlation with a clinical endpoint or surrogate, but fail as a predictive tool.

Another more recent study evaluated the sensitivity and specificity of elevated serum creatinine as a predictor of early histological changes of CAN.[23] In that study, surveillance biopsies were obtained from 289 patients 6 to 12 months after kidney transplantation. Receiver operator characteristic curve (ROC) plots were generated for serum creatinine levels and eGFR using either 'mild changes' (Banff '97 score of ≥1) or 'moderate changes' (Banff '97 score of ≥2) for each of the ten histological measurements as the diagnostic gold standard. AUROC values ranged from 0.51 (representing no discrimination) to 0.62, and most of the 95% confidence intervals included or were close to 0.5, indicating that neither serum creatinine nor eGFR had predictive value for any of the individual histological parameters, with the exception of interstitial inflammation (i). Thus, the results of these studies suggest that serum creatinine and eGFR have a limited clinical role in predicting the early histopathological changes that precede CAN and should not be used for this purpose; they have been adopted prematurely as surrogates or predictive markers of CAN.

The ultimate criterion for assessing the benefit of markers for a pathological condition is whether they add information beyond that otherwise available and whether this information leads to a change in management that is ultimately beneficial to the patient.[24] Despite the obvious attraction of using functional markers as predictors or surrogates for CAN, if they cannot discriminate between clinically relevant subclasses of patients (those with normal/abnormal early histopathology[23] or those who will/will not have allograft failure at 2 years[22]), they have a limited predictive role.

3. Calcineurin Inhibitor Nephrotoxicity

CNIs such as ciclosporin (cyclosporine) and tacrolimus have led to substantial improvements in early transplant results, primarily by reducing early severe acute rejections. However, CNIs may cause both acute and chronic nephrotoxicity. CNI nephrotoxicity occurs in two phases, each with distinct histological and clinical (functional) characteristics. The acute phase is reversible, typically occurring within the first year after transplantation, and is accompanied by functional nephrotoxicity (rise in serum creatinine and decrease in renal function), high ciclosporin levels, isometric vacuolization of the proximal tubules and mild arteriolar hyalinosis. An important feature of acute nephrotoxicity is its rapid and significant reversal when CNI dosage is reduced.[25] The classical histological lesions associated with CNI nephrotoxicity have been well described and include *de novo* or progressive arteriolar hyalinosis, focal areas of tubular atrophy, striped interstitial fibrosis and tubular microcalcification.[26,27] To gain an understanding of the histological evolution of chronic CNI nephrotoxicity, Nankivell and colleagues[28] evaluated the effects of CNI nephrotoxicity in a long-term prospective, protocol biopsy study. The investigators examined 888 biopsy samples taken regularly over a 10-year post-transplant period from 99 ciclosporin-treated patients. The study found that the prevalence of CNI-associated lesions increased with time after transplantation; the 1- and 5-year prevalences were 61% and 90%, respectively, for *de novo* or increasing arteriolar hyalinosis, 35% and 70% for striped fibrosis, and 44% and 68% for tubular microcalcification. At 10 years, these numbers increased, with 100% of patients having arteriolar hyalinosis, 88% having striped fibrosis, and 79% having tubular microcalcification. The chronic phase was by definition persistent, being observed in serial biopsies over a minimum 2-year period, occurred at a median onset of 3 years, and was usually irreversible and associated with severe hyalinosis and progressive glomerulosclerosis (figure 1). However, it is possible that not all of these lesions are attributable to CNI use, as the study did not include a CNI-free control group.

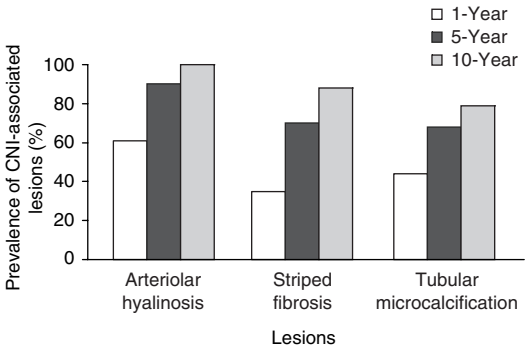

Fig. 1. Prevalence of calcineurin inhibitor (CNI)-associated lesions in 888 prospective protocol kidney biopsy specimens from 99 patients taken regularly until 10 years after transplantation for evidence of ciclosporin (cyclosporine) nephrotoxicity.[28]

4. Calcineurin Inhibitor Withdrawal/ Conversion Strategy

Sirolimus is a potent immunosuppressive agent with a novel mechanism of action. It is a macrocyclic lactone antibiotic that binds to mammalian targets of rapamycin, inhibiting T and B cell proliferation but having no effect on calcineurin activity. Withdrawing a CNI from a sirolimus-based regimen or converting from a CNI to sirolimus are strategies that have been increasingly used to reduce CNI-related nephrotoxicity and potentially improve long-term graft outcomes. A recent systematic review by Mulay and colleagues[29] examined studies comparing patients who received a planned withdrawal of a CNI from their sirolimus-based regimen and those who continued to receive a CNI. Eight studies reporting on six randomized, controlled trials (RCTs) involving 1047 patients were identified (table I). Five of the trials used ciclosporin and one used tacrolimus. Pooled data from three homogeneous trials (n = 714) indicated that withdrawal of the CNI significantly increased the risk of acute rejection (relative risk [RR] 2.36; 95% CI 1.34, 4.15; p = 0.003) and had no significant effect on the risk of graft loss. However, pooled data from five homogeneous trials (n = 1007) evaluating renal function at 1 year, measured using creatinine clearance, demonstrated that renal function was significantly higher in the CNI-withdrawal group than in the group receiving continued CNI and sirolimus therapy (weighted mean difference [WMD] 7.5 mL/min; 95% CI 5.1, 9.9; p < 0.00001). Pooled data from three homogeneous studies (n = 557) demonstrated a significant reduction in the proportion of patients with hypertension in the CNI-withdrawal group compared with the group receiving continued CNI therapy (RR 0.56; 95% CI 0.40, 0.78; p = 0.0006).

Results at 36 and 48 months for one large RCT included in the 2005 Mulay et al. systematic review have recently been reported.[36,37] Patients in the trial were receiving triple therapy with a sirolimus-ciclosporin-corticosteroid regimen. At 3 months, patients were randomly assigned to remain on triple therapy (n = 215) or have ciclosporin withdrawn (n = 215). At 36 months, renal histology, evaluated using the CADI scoring system in patients who remained on therapy and underwent serial biopsies, was significantly better in patients receiving sirolimus-corticosteroid therapy (n = 32) than in those also receiving ciclosporin (n = 31; mean CADI score 4.70 vs 3.20; p = 0.003).[36] Furthermore, in these patients, the Nankivell GFR[38] was also significantly better in the sirolimus-corticosteroid group than in the triple-therapy group at 36 months (54.8 vs 68.2 mL/min; p = 0.009). Estimating GFR using the Nankivell formula is limited, however, by the inferior performance that it has shown compared with other techniques used to either measure or estimate GFR.[39] At 48 months (n = 97 for triple therapy group and n = 112 for dual therapy group), graft survival was significantly higher in the sirolimus-corticosteroid group than in the group receiving triple therapy (96% vs 91%; p = 0.026, when death with a functioning graft was excluded; or, 92% vs 84%; p = 0.024, when death with a functioning graft was included) [figure 2].[37] Moreover, creatinine clearance, GFR and mean arterial blood pressure were also significantly improved in patients for whom ciclosporin was withdrawn. A post-hoc analysis of the 48-month data was performed by Russ et al.[40] to determine whether the benefits in renal function observed with ciclosporin withdrawal differed according to baseline renal function. Results of the analysis showed that improvements in renal function are observed regardless of baseline

Table I. Target drug levels and other immunosuppression in the studies included in a systematic analysis of randomized trials involving calcineurin inhibitor (CNI) withdrawal from a sirolimus-based immunosuppressive regimen[29]

Study cohort	Target sirolimus levels (ng/mL)		Target CNI levels (ng/mL)		Other immunosuppression
	before withdrawal	after withdrawal	before withdrawal	after withdrawal	
Gonwa et al.[30]					
Withdrawal (n = 100)	10–20	10–20	100–175 then 100–150	NA	Induction: NR
Control (n = 97)	Fixed dose (6-mg load then 2 mg/day)	Fixed dose (6-mg load then 2 mg/day)	200–400 then 200–300	150–250	Both groups: prednisone
Baboolal[31]					
Withdrawal (n = 42)	4–12	8–16	200–400 then 125–250	NA	Induction: not used
Control (n = 45)	4–12	8–16	200–400 then 125–250	50–100	Both groups: prednisone
Johnson et al.[32]					
Withdrawal (n = 215)	>5	20–30	200–400 then 150–300	NA	Induction: not used
Control (n = 215)	>5	>5	200–400 then 150–300	75–200	Both groups: prednisone
Stallone et al.[33]					
Withdrawal (n = 20)	Fixed dose (15-mg load then 2 mg/day)	10–15	150–250	NA	Induction: NR Both groups: prednisone
Control (n = 20)	Fixed dose (15-mg load then 2 mg/day)	Fixed dose (2 mg/day)	150–250	150–250	
Jardine[34]					
Withdrawal (n = 101)	4–12	8–16	125–250	NA	Induction: NR
Control (n = 105)	4–12	8–16	125–250	50–100	Both groups: prednisone
Grinyo et al.[35]					
Withdrawal (n = 44)	8–16	12–20	3–8	NA	Induction: not used
Control (n = 43)	4–8	4–8	8–12	5–10	Both groups: prednisone

NA = not applicable; **NR** = not reported.

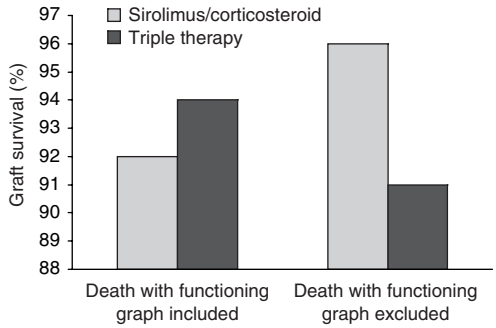

Fig. 2. Graft survival at 48 months among renal transplant patients receiving a triple regimen of ciclosporin (cyclosporine), sirolimus and corticosteroid (n = 97), and those receiving sirolimus and corticosteroid alone (n = 112).[37]

renal function, with the benefit being most marked in patients with a baseline calculated GFR of ≤45 mL/min. The percentage of patients completing 4 years of treatment was higher in the sirolimus-corticosteroid group. The limitation of this study is that an adverse event was the principal reason for discontinuation and many feel the use of full-dose ciclosporin and sirolimus increased the nephrotoxicity in the control group.

Another recent systematic review looked at studies of converting from a CNI to a sirolimus regimen.[41] RCTs included in the review were studies comparing patients initially treated with a CNI and then switched to sirolimus (with complete removal of the CNI) with patients maintained on CNI therapy. For studies to be included in the review, the indication for conversion had to be either histological confirmation of CAN and/or chronic CNI toxicity and/or decreased renal function presumed to be due to CAN. Five RCTs with a total of 1040 patients were included in the systematic review. Pooled data from four heterogeneous studies (n = 917) showed that mean creatinine clearance significantly improved after conversion to sirolimus (WMD 6.4 mL/min; 95% CI 1.9, 11.0]; p = 0.003). However, results of the review also suggested that sirolimus was associated with a high discontinuation rate.

Eighteen-month results for a large RCT included in the 2006 Mulay et al. systematic review were recently presented at the 2006 World Transplant Congress.[42] In this trial, 830 patients receiving CNI therapy were randomly assigned, in a 1 : 2 ratio, to continue with a CNI or to convert from the CNI to sirolimus. Patients were eligible for the trial if they received a kidney transplant between 6 months and 5 years before enrolment. Rates of acute rejection, graft survival and patient survival were not significantly different between the two treatment groups; nor was GFR in the whole group. However, mean GFR in the sirolimus group was significantly higher than in the CNI group in patients with a baseline GFR >40 mL/min and without significant proteinuria at entry (Nankivell GFR 63.5 vs 61.0 mL/min; p = 0.005). After the 6-month timepoint there was no significant difference between the two study groups in the incidence of treatment-related adverse events; however, there was a high withdrawal rate in both groups.

Recently, interim 1-year results of the Spare-the-Nephron trial were presented at the 2007 American Transplant Congress.[43] This 2-year multicentre RCT is comparing renal function in kidney transplant patients receiving maintenance immunosuppression with mycophenolate mofetil (MMF) and sirolimus with those receiving an MMF and CNI regimen. Patients were randomized to one of the two study groups at 1–6 months post-transplant. A total of 208 of 305 patients completed 1-year follow-up, and results demonstrated a trend towards improved renal function in the MMF + sirolimus group compared with the MMF + CNI group (median percentage change from baseline in measured GFR 18.5 vs −4.4). However, complete follow-up data are required to provide definite statements regarding differences between these two treatment regimens.

5. Calcineurin Inhibitor Avoidance Strategy

A number of studies have evaluated a CNI-free regimen in kidney transplant recipients (table II). A recent study by Larson et al.[44] randomly assigned 165 patients to receive triple therapy with either sirolimus, MMF and corticosteroids (n = 81); or tacrolimus, MMF and corticosteroids (n = 84), both groups also receiving thymoglobulin. At 1 year, there were no significant differences between the

Table II. Randomized controlled trials evaluating a calcineurin inhibitor-free regimen in kidney transplant recipients

Intervention	Outcomes
Larson et al.[44] (n = 165)	
Patients randomized 1 : 1 to receive: Sirolimus + MMF + corticosteroids (n = 81) Tacrolimus + MMF + corticosteroids (n = 84)	Patient survival, graft survival, acute rejection and renal function not significantly different between groups at 1 year
Hamdy et al.[45] (n = 132)	
Patients randomized 1 : 1 to receive: Tacrolimus + sirolimus (n = 65) MMF + sirolimus (n = 67)	Patient survival, graft survival and acute rejection not significantly different between groups at 2 years Significantly better renal function at 2 years in the MMF + sirolimus group compared with the tacrolimus + sirolimus group (creatinine 106.1 vs 123.8 μmol/L; p = 0.017; GFR 94.9 vs 79.6 mL/min; p = 0.005)
Flechner et al.[46] (n = 61)	
Patients randomized 1 : 1 to receive: Sirolimus + MMF + corticosteroids (n = 31) Ciclosporin + MMF + corticosteroids (n = 30)	Patient survival, graft survival and acute rejection not significantly different between groups at 1 year Significantly better renal function at 2 years in sirolimus group compared with ciclosporin group (Cockroft-Gault GFR 80.4 vs 63.4 mL/min; p = 0.008)
Flechner et al.[47,48] (n = 450)	
Patients randomized 1 : 1 to receive: Group 1: sirolimus 8–15 ng/mL + tacrolimus 6–15 ng/mL through week 13, followed by elimination of tacrolimus and increase in sirolimus to 12–20 ng/mL (n = 155) Group 2: sirolimus 10–15 ng/mL through week 26, 8–15 ng/mL thereafter + MMF up to 2 g/day (n = 155) Group 3 (control): tacrolimus 8–15 ng/mL through week 26, 5–15 ng/mL thereafter + MMF up to 2 g/day (n = 140)	Patient survival not significantly different among groups at 18 months Acute rejection rates significantly different between groups 2 and 3 (p < 0.001), but not between groups 1 and 3 (p = 0.133) Graft survival significantly different between groups 1 and 3 (p = 0.038) Group 2 terminated in June 2006 owing to higher than expected acute rejection rates No significant difference in renal function among groups at 18 months

GFR = glomerular filtration rate; **MMF** = mycophenolate mofetil.

two study groups in patient survival, graft survival, acute rejection or renal function. The incidence of chronic histological lesions, measured using the Banff scoring system, was also similar between the two treatment regimens, with the exception of chronic vascular changes, which were significantly higher in the group receiving a CNI (43% vs 26%; p = 0.03).

A study by Hamdy et al.[45] randomly assigned patients to receive either a tacrolimus-sirolimus regimen (n = 65) or an MMF-sirolimus regimen (n = 67). Patient survival, graft survival and CADI scores of protocol biopsies were not significantly different between the two treatment groups. Interestingly, the incidence of vascular intimal thickening was significantly higher within the MMF-sirolimus regimen. However, at 2 years, significantly better renal function was observed in patients receiving MMF-sirolimus than in those receiving tacrolimus-sirolimus (creatinine 106.1 vs 123.8 μmol/L; p = 0.017; GFR 94.9 vs 79.6 mL/min; p = 0.005). A study by Flechner et al.[46] randomly assigned patients being treated with MMF and corticosteroids (n = 61) to receive either sirolimus or ciclosporin. At 2 years, patients receiving sirolimus had significantly better renal function than those receiving ciclosporin (Cockroft-Gault GFR 80.4 vs 63.4 mL/min; p = 0.008).[49] Furthermore, the number of normal biopsies, according to the Banff classification system, was significantly higher in the sirolimus group than in the ciclosporin group (67% vs 21%; p = 0.013). There were also significantly more biopsies receiving grade II and III Banff CAN scores in the ciclosporin group than in the sirolimus group (37.5% vs 12.5%; p = 0.013).

Although results from these three studies[44-46] do not show differences in patient survival, graft survival or acute rejection with sirolimus, they do suggest that renal function is improved with the sirolimus regimen. However, the SYMPHONY trial, a 1-year, open-label RCT with four parallel arms, found that renal function and acute rejection were significantly

better in patients receiving low-dose tacrolimus compared with those receiving either a standard dose of ciclosporin, a low-dose regimen of sirolimus, or a low-dose regimen of ciclosporin.[50] Patients (n = 1645) were also treated with MMF and corticosteroids, and those in the low-dose groups underwent induction treatment with daclizumab. However, the dosage of sirolimus used in this study is below that recommended, so it is not the ideal study of CNI avoidance with sirolimus.

In the ORION study, *de novo* renal allograft patients were randomly assigned to either sirolimus 8–15 ng/mL plus tacrolimus 6–15 ng/mL through week 13, followed by elimination of tacrolimus and an increase in the sirolimus dose to 12–20 ng/mL thereafter; sirolimus 10–15 ng/mL through week 26, followed by sirolimus 8–15 ng/mL thereafter plus MMF up to 2 gm/day; or tacrolimus 8–15 ng/mL through week 26, followed by tacrolimus 5–15 ng/mL + MMF up to 2 gm/day. All patients received two doses of daclizumab (2 mg/kg) and corticosteroids.[47,48] At 18 months, the interim analysis showed that despite a higher rate of acute rejections in the sirolimus plus MMF group, resulting in the termination of this arm of the study, renal function was numerically (but not statistically) better at 18 months, suggesting that in the setting of CNI-free immunosuppression, mild acute rejection is not associated with deterioration of renal allograft function, as reflected by GFR, serum creatinine and urinary protein excretion.[47,48]

Based on results of recent clinical trials, the use of sirolimus, MMF and corticosteroids is not recommended in combination with interleukin (IL)-2-receptor antibody (basiliximab) induction in the *de novo* organ transplant setting. An investigational clinical trial compared renal function at 12 months in *de novo* renal transplant recipients receiving sirolimus plus MMF plus corticosteroid versus ciclosporin plus MMF plus corticosteroid regimen from the time of transplantation. All participants received a course of basiliximab. The trial was terminated when interim results revealed a higher than expected rate of acute rejection and did not support a renal function benefit in renal transplant patients receiving basiliximab in combination with sirolimus plus MMF plus corticosteroids, relative to the control group. Owing to this fact, as well as to our local experience, the inclusion of sirolimus in a maintenance regimen in our centre is postponed to 6 months after the surveillance biopsy is performed, as described in detail in section 6.

6. Calgary Transplant Program Experience

Since 1998, the Calgary Transplant Program performs a surveillance biopsy at approximately 6–12 months after kidney transplantation, as well as at the time of the transplantation for baseline. Excluded patients are those with biopsy contraindications (those with a transplant placed in their peritoneal cavity, receiving anticoagulants, or who are a Jehovah's Witness) and those who refuse the biopsy. During this period, the standard induction regimen consists of an anti-IL-2-receptor monoclonal antibody for patients not considered to be at high immunological risk. Polyclonal induction is used for those considered at high immunological risk or patients who experience delayed graft function (need for dialysis more than 24 hours after the transplantation). Standard maintenance therapy comprises a triple therapy regimen of a CNI (currently tacrolimus), an antiproliferative agent (mycophenolate sodium [MPS] or MMF) and prednisone.

After the surveillance biopsy is performed, major drug regimen changes are made based on the chronic histological damage in the kidney, even though the patient may have normal/stable kidney function. Previously, patients with a CADI score >4 have been identified as having increased risk of graft loss at 3 years;[51] therefore, this is used as the threshold for defining a level of CAN severity that is associated with short-term allograft loss. Thus, when the CADI score is >4, the CNI (currently tacrolimus) is discontinued and sirolimus is added so that the patient is maintained on prednisone, sirolimus and MMF. If the score is between 2 and 4, the tacrolimus dose is reduced (aiming for a level of 3–5 ng/L) and MMF is replaced with sirolimus. If the CADI score is <2, the existing maintenance therapy is continued

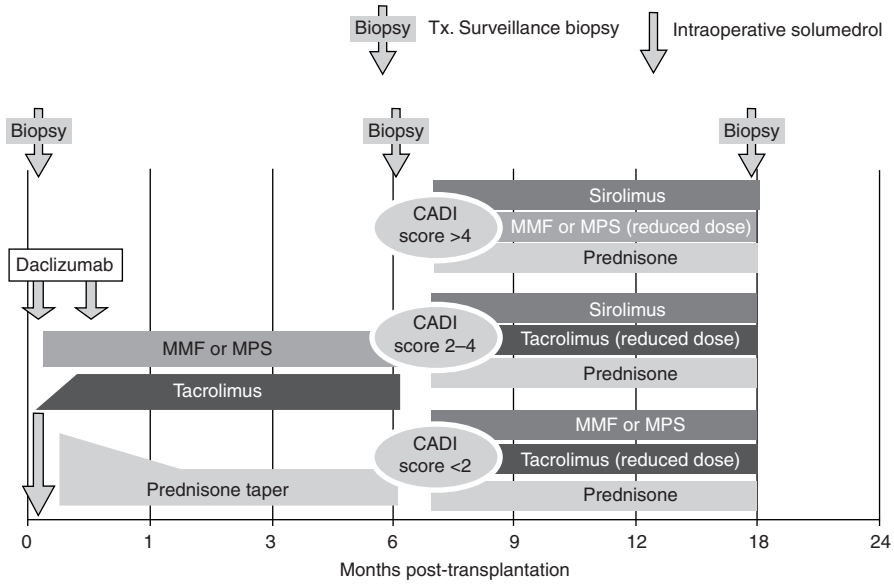

Fig. 3. Post-transplantation treatment algorithm. **CADI** = Chronic Allograft Damage Index; **MMF** = mycophenolate mofetil; **MPS** = mycophenolate sodium; **Tx.** = transplant.

and the biopsy repeated 1 year later (figure 3). The treatment algorithm described above is then reapplied to the results of this biopsy. Plans to analyse and report on this experience are currently under way.

Although the risk of significant complications following renal biopsy has decreased over the years, particularly with the use of ultrasound guidance[52] and automated core biopsy systems,[53] there are still potential risks.[54-56] The frequency of post-biopsy complications such as macrohaematuria (0.8–3.5%), haematoma (2.2–2.6%) and arteriovenous fistula (2.4–9%) shows considerable variation.[54-56] The ultrasound-guided percutaneous renal biopsy with an automated biopsy device has been used in our institution for almost 20 years.[53] In the past 10 years we have performed approximately 2000 transplant kidney biopsies. Our radiologist obtained satisfactory amounts of kidney tissue in almost all cases with a lower complication rate than the literature (unpublished data). The benefit of surveillance biopsies has not been quantified other than detecting subclinical CAN and the strategy has yet to be widely implemented. We think that the potential benefit to a patient is greater than the risks.

7. Conclusions

CAN represents the main cause of late kidney transplant failure and is associated with a number of clinical risk factors. Regardless of the obvious appeal of using functional biomarkers as predictors of CAN, evidence suggests that composite histological indices based on data from surveillance biopsies are the best way to predict long-term graft outcomes. CNIs have led to major improvements in early transplant outcomes, but strategies that taper their use could lead to improved results in the long term.

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