Managing the Failing Allograft

Elizabeth A. Kendrick and Connie L. Davis
Department of Medicine, Division of Nephrology, University of Washington School of Medicine, Seattle, Washington

ABSTRACT

Managing the failing allograft juxtaposes immunosuppressive management and routine chronic kidney disease care. The complications of immunosuppression can be more pronounced in those with renal failure (infection, anemia, bone disease). The withdrawal of immunosuppression may be associated with acute allograft rejection, arthralgias, and the development of antidonor antibodies. Likewise depression is prevalent. Improving well-being and overall survival necessitates proper titration of immunosuppressive medications and control of blood pressure, anemia, lipids, and glucose along with attention to treatment of depression.

Despite advances in the field of transplantation resulting in a lower incidence of rejection leading to early graft failure, long-term function of kidney transplants arguably has been less positively impacted. Recipients of kidney transplants are left with a graft with a finite life span and their longer term care will focus on problems related to a failing transplant. Transplant recipients with failing renal allografts may require modulation of immunosuppression, which can reduce the rate of graft dysfunction in some instances. These patients should also be treated analogous to patients with chronic kidney disease (CKD) as the glomerular filtration rate (GFR) of most allograft recipients is less than 60 cc/min (1–3). This can involve therapy for complications related to the failing allograft as well focused toward preserving allograft function. Even so, little proof yet exists that the measures shown to decrease the progression of native kidney disease will retard allograft loss (4).

The most common cause of allograft failure is chronic allograft nephropathy (CAN) (5,6). The histologic findings of CAN are chronic interstitial fibrosis and tubular atrophy with or without fibrointimal vascular thickening. Glomerular changes described as membranoproliferative glomerulonephritis or focal sclerosis with prominent basement membrane thickening without immune deposits may also be present. Protocol biopsy studies have shown the development of mild CAN by 12 months after transplant in 94.2% and moderate CAN by 10 years in 95% (Fig. 1) (5,6).

The etiology of CAN is multifactorial and includes preexisting allograft age-related renal damage, ischemic injury at transplant, immunologic injury, and calcineurin inhibitor (CNI) toxicity (Table 1) (5,6). CNIs promote profibrotic cytokines and oxidative stress that can enhance allograft scarring (7,8). Clinically a slow increase in serum creatinine, hypertension, and mild to severe proteinuria may be noted (1,2,4,9). Occasionally the presentation is more acute, with a rapid increase in the serum creatinine and nephrotic range proteinuria. Once established, the glomerular and tubulointerstitial damage seen with CAN is irreversible and results in declining renal function and eventual graft failure.

Nonimmunologic factors that are associated with the development and progression of CAN can be viewed as somewhat analogous to those contributing to CKD in native kidneys. For example, there is extensive literature supporting the benefit of therapy aimed at lowering blood pressure (BP) and urine protein excretion in both diabetic and nondiabetic native renal disease. High BP, lipid, and other metabolic abnormalities are common in transplant recipients and have been shown to have a similar impact in patients with transplanted kidneys as has been seen in native kidney disease. Medical intervention targeting factors associated with the progression of graft dysfunction have in some instances been shown to prolong graft life, although not to the same degree of certainty as in native renal disease.

Because multiple factors impact the development of CAN, the earlier the predominant factor can be determined the better. If CNI toxicity is not suspected, obstruction is ruled out, and blood volume is normal, a biopsy should be done. There may often be a pattern of oscillating creatinine values that predate the diagnosis of chronic rejection, CNI toxicity, or CAN. The earlier histologic confirmation is obtained, the sooner specific treatment may be provided, hopefully with less resultant fibrosis.

There is increasing recognition that the level of GFR provided by a kidney transplant will often fulfill the definition of CKD, even with what appears to be relatively well-preserved function. Transplant recipients with a

Address correspondence to: Connie L. Davis, MD, Box 356174, 1959 NE Pacific St., Seattle, WA 98195, or e-mail: cdavis@u.washington.edu.

Seminars in Dialysis—Vol 18, No 6 (November–December) 2005 pp. 529–539

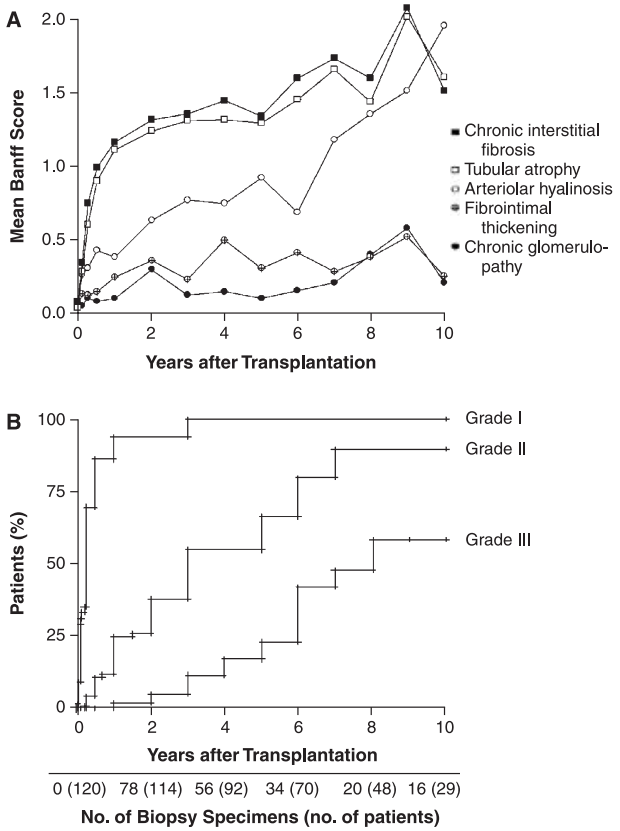

FIG. 1. Mean Banff scores for chronic interstitial fibrosis, tubular atrophy, arteriolar hyalinosis, chronic fibrointimal thickening and chronic glomerulopathy (panel a) and prevalence of mild (grade I), moderate (grade II), and severe (grade III) chronic allograft nephropathy according to the Banff criteria (panel B). The damage reflected by the Banff scores contributed to chronic allograft nephropathy, whose cumulative actuarial prevalence (1—Kaplan-Meier survival estimate) was defined according to the histologic findings on sequential biopsy specimens obtained according to the protocol and classified according to the Banff criteria. The number of biopsy specimens (and patients) at risk are given below the figure. (Reprinted with permission from Nankivell et al., *N Engl J Med* 349:2326–2333, 2003).

failing allograft should be evaluated and treated for secondary complications such as anemia, cardiovascular risk factors, calcium and phosphate imbalance, and metabolic bone disease as aggressively as is recommended for CKD patients. What follows is a discussion of complications associated with the failing renal allograft and what interventions can modify both the course of the transplant as well as the overall course of the patient.

Immunosuppression

The selection of immunosuppressive agents in the failing allograft is determined by the level of renal function along with patient comorbidities and tolerance. When considering modification of immunosuppression in those with interstitial fibrosis, one should ask about the predominant etiology, if determinable. If due to CNIs and the serum creatinine is 3.0 mg/dl, then consider conversion to sirolimus while maintaining mycophenolate mofetil

TABLE 1. Reported risk factors for chronic allograft nephropathy

Immunologic
Acute rejection
Late acute rejection
Histocompatibility mismatch
Prior sensitization
Suboptimal immunosuppression
Noncompliance with immunosuppressive medications
Injury
Ischemic injury and delayed graft function
Older donor age
Donor and recipient size matching
Calcineurin inhibitor toxicity
Hyperlipidemia
Hypertension
Cigarette smoking
Hyperhomocysteinemia
Oxygen free radicals
Infection (cytomegalovirus [CMV]/Epstein-Barr virus [EBV])
Proteinuria

(MMF) and prednisone (10,11). Side effects associated with this conversion are listed in Table 2. Conversion to sirolimus in the setting of CAN appears to be most beneficial in preserving graft function when renal dysfunction and pathologic abnormalities are less severe (12), when CNIs are withdrawn completely (13), and proteinuria is low grade (less than 800 mg/day) (14).

Several centers have reported prolongation of renal graft survival in this setting with the addition of MMF concurrent with a reduction in or discontinuation of CNIs (15–19). Alternatively, conversion from MMF to leflunomide has in a nonrandomized fashion been reported to stabilize renal function. If ongoing rejection is the issue, then convert the patient to tacrolimus. If the patient is already on tacrolimus and MMF, there is no proven therapy, and the addition of antilymphocyte preparations or augmentation of tacrolimus dosing needs to be put into the context of patient risk (infection, malignancy, cardiovascular disease) and the amount of remaining renal parenchyma. However, intravenous immunoglobulin (IVIg) therapy could be tried, although there is a risk for acute renal failure and cardiac events, especially with the use of products with a sucrose base (20).

Hypertension

Although remission of hypertension after renal transplantation has been reported (21), the majority of transplant recipients require antihypertensive therapy (22,23). Impaired function of the renal graft is associated with posttransplant hypertension, although hypertension can

TABLE 2. Most frequent side effects on conversion from calcineurin-based to sirolimus-based immunosuppression for CAN

Hyperlipidemia
Anemia
Diarrhea
Leukopenia
Thrombocytopenia
Edema

TABLE 3. Antidepressant use in the setting of chronic renal failure and calcineurin inhibitor use

Drug	P-450 metabolized	Dose adjusted for liver disease	Dose adjusted for kidney disease	Dose with a creatinine clearance of 20–30 ml/min
Fluoxetine (Prozac)[a] Serotonin reuptake inhibitor (SSRI)	2C19, 2D6	Yes	No	20–40 mg/day
Paroxetine (Paxil) (SSRI)	2D6, careful with β-blocker administration	Yes	Yes	10–40 mg/day
Citalopram (Celexa) (SSRI)	2C19, 2D6, 3A4	Yes	Yes (moderate to severe)	No specific recommendations
Escitalopram (Lexapro) (SSRI)	3A4, 2D6, 2C19	Yes	Yes	
Sertraline (Zoloft) (SSRI)	3A4 but little inhibition, 2D6	Yes	Yes	
Fluvoxamine (SSRI)	1A2, 2D6, 2C19, 2C9, 3A4	Yes	No	
Venlafazine (Effexor)	2D6, 3A4 but little inhibition, 2C19	Yes	Yes	
Bupropion (Wellbutrin) (Norepinephrine-Dopamine reuptake inhibitor)	2B6, 2D6	No		
Mirtazpine (Remeron) (α_2-adrenergic receptor antagonist; SRA)	2D6, 1A2, 3A4, 2C9	Yes	Yes	
Nefazodone (serotonin receptor antagonists, SRA)	3A4, 2D6	Yes, with extreme caution	No	
Trazadone (SRA)	3A4, 2D6, little effect on 3A4	No	No for parental compound, questions about metabolites	

[a] Fluoxetine is a weak inhibitor of 3A4 and there have been reports of increased cyclosporine levels in the literature.

be present even in the face of good function. Several factors contribute to this, including renin-mediated hypertension related to the native kidneys, obesity, and genetic factors. In addition, specific immunosuppressive drugs may enhance the incidence of hypertension after transplantation. Hypertension caused by the CNIs cyclosporine and tacrolimus appears to be mediated by renal vasoconstriction (24,25); sodium and water retention due to renal dysfunction and corticosteroids may also contribute. Patients are less likely to be hypertensive if their immunosuppressive drug regimen does not include a CNI (22). The impact of renal denervation following transplantation with loss of renoprotective autoregulation may also play a role in hypertensive transplant injury.

Several studies have demonstrated an association between posttransplant hypertension and risk of chronic kidney graft failure (22,26–28). A striking association between systolic BP and subsequent kidney graft survival has been reported in a large multicenter study involving nearly 30,000 patients transplanted between 1987 and 1995 (26). Risk of renal graft failure was incrementally increased above a systolic BP of 140 mmHg; there was a greater than twofold risk of graft loss for systolic BP readings of ≥ 180 mmHg. This observation was independent of other factors known to impact kidney transplant outcome: patient age, race, original cause of renal disease, type of hypertension treatment, cold ischemic time, preformed panel reactive antibodies (PRAs), and human leukocyte antigen (HLA) mismatches.

The North American Pediatric Renal Transplant Cooperative Study (NAPRTCS) reported a very high incidence of antihypertensive treatment after transplant, particularly in Blacks (27). The use of medications to treat hypertension decreased by 5 years after transplant, but was still present in the majority of patients. There was a 1.5- to 2-fold risk of graft loss in the presence of treated hypertension; the risk of graft loss was nearly 3-fold if the patient also required treatment for acute rejection.

What is the Goal for Treatment?

Blood pressure is a continuous variable. Exemplifying this concept is the introduction in the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7) of a category of prehypertension or "high normal blood pressure" values between 130 mmHg and 139 mmHg (29). Although the adverse effect of hypertension on renal allograft function has been well documented, there is controversy about an additional benefit of lowering BP below the defined cutoff of hypertension (i.e., less than 140/90 mmHg). However, it seems reasonable to treat a patient with a failing renal allograft as a patient with CKD, with respect to BP lowering goals. Targeting lower BP goals has been shown to be effective in slowing the progression of renal dysfunction in CKD patients with significant proteinuria as well as those with diabetic renal disease with or without heavy proteinuria (30). Patients with CKD without significant proteinuria do not seem to have an additional benefit on progression of renal dysfunction with lower BP goals, but there is a benefit in terms of cardiovascular risk (31). Because CKD patients have an elevated risk for cardiovascular events, treatment of hypertension to achieve a BP of less than 130/80 mmHg is recommended by JNC 7 as well as the recent Kidney Disease Outcomes Quality Initiative (K/DOQI) guidelines (30). A target BP of less than 125/75 mmHg is recommended for those patients with more than 1 g of proteinuria per day. This approach is also recommended for transplant patients with chronic allograft dysfunction.

Impact of Proteinuria

Proteinuria is associated with an increased risk of renal failure and progression of renal dysfunction in patients with both diabetic (32) and nondiabetic kidney disease (33) independent of BP. Reduction in proteinuria

has been shown to decrease the rate at which renal function declines (34). This is most often achieved by the use of angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs). The association between proteinuria and progressive renal failure has also been shown in patients with renal allografts (35–37). Proteinuria can be secondary to recurrent or de novo glomerular disease, but most commonly is related to chronic allograft nephropathy. While long-term studies do not exist documenting improved outcomes in chronic allograft dysfunction with treatment targeting proteinuria, it seems reasonable to extrapolate the benefit seen in chronic native renal disease to those with kidney transplants (38–40).

What Hypertension Agent Should be Used in Renal Transplant Patients?

All classes of antihypertensive agents are effective in treating hypertension in the transplant recipient, although more than one drug is often required. Moreover, it seems most important that the goals of BP treatment are achieved rather than which specific agent is used. That being said, specific agents may have additional benefits beyond BP control. ACE inhibitors and ARBs have a greater effect on reducing proteinuria, while calcium channel blockers can minimize some of the nephrotoxic effects of CNIs. The use of β-blockers may be required for cardiac indications. In addition, drug interactions and side effect profiles can play a major role in the selection of antihypertensive drug selection.

Calcium Channel Blockers. Both dihydropyridine and nondihydropyridine types of calcium channel blockers (CCBs) effectively lower BP (41). CCBs have been shown to have an antagonistic effect on renal vasoconstriction caused by CNI, which may help prevent chronic CNI nephrotoxicity (42). CCBs of both classes have been shown to be renoprotective when used early after transplantation and this effect is independent of BP reduction (43,44). The mitigation of CNI nephrotoxicity appears related to renal vasodilation. Short- to medium-term renal function is improved (43–46) and the degree of interstitial fibrosis is lessened (47) by the use of CCBs. Whether CCBs have a renoprotective effect on already established CAN apart from BP control has not been studied. Extrapolating from the use of CCBs in CKD, there does not appear to be a more rapid progression of renal dysfunction as compared to other classes of antihypertensive agents (apart from antagonists of the renin-angiotensin system). However, as nondihydropyridine calcium antagonists (verapamil or diltiazem) may also have an antiproteinuric effect apart from BP control, future investigation is warranted (41).

Dihydropyridine calcium antagonists (e.g., amlodipine, felodipine) have a lesser mitigating effect on proteinuria, if at all. These drugs can increase proteinuria as a result of diminished renal autoregulation (renal afferent vasodilation, increased glomerular hydrostatic pressure and filtration fraction) (48). Side effects such as peripheral edema and gingival hyperplasia when used with cyclosporine may also limit the desirability of dihydropyridine CCBs (49).

The nondihydropyridine CCBs interfere with hepatic metabolism of CNIs and have been used to decrease the dose of these medications. However, use in this setting is meant more to reduce cost expenditure than (50) reduce exposure to the drug, as overall drug exposure is the same in each instance.

ACE Inhibitors and ARBs. ACE inhibitors and ARBs have been studied extensively in CKD and their use results in amelioration of proteinuria and a slower rate of loss of renal function, particularly in diabetic nephropathy. The combined use of the two agents appears to have an additive effect (51). In renal transplant recipients, there seems to be comparable benefit, as the use of ACE inhibitors and ARBs has been shown to decrease proteinuria by 30% to more than 50% (38,39,48,52). These drugs decrease intraglomerular pressure, but also have a separate effect on glomerular permselectivity (53)—both mechanisms contribute to an improvement in protein excretion.

In kidney transplant patients, there may be some reluctance to use ACE inhibitors and ARBs because of concerns about causing an increase in the serum creatinine (especially if transplant renal artery stenosis is present), worsening anemia, and precipitating hyperkalemia. Moreover, the use of CNIs in renal transplant recipients is often associated with sodium excess and a low renin state such that ACE inhibitors and ARBs might be thought to be less effective in this group of patients. However, ACE inhibitors and ARBs are just as effective at lowering BP in these patients as other classes of antihypertensive agents, and are usually well tolerated.

ACE inhibitor and ARB use decreases intraglomerular pressure and filtration fraction and may cause an increase in the serum creatinine. However, short-term stability of renal transplant function with the use of ACE inhibitors and ARBs has been demonstrated (38,54,55). The effect of these drugs on long-term renal transplant function in the setting of CAN has not been as well studied (56); however, two recent retrospective studies have shown improved graft survival in patients with established CAN when they were treated with ACE inhibitors or ARBs (57,58). It should be noted that if a significant decline in renal graft function occurs, evaluation for stenosis of the renal transplant artery is warranted. Hyperkalemia developing after initiation of ACE inhibitors or ARBs can usually be managed by dietary restriction, diuretics, or Kayexalate. Anemia is not uncommon with the use of these agents (59). It is usually mild and responds to treatment with erythropoietin.

Up-regulation of transforming growth factor (TGF)-β in renal allografts is associated with initiation and progression of CAN through induction of tubulointerstitial fibrosis and arteriolopathy by stimulating extracellular matrix protein synthesis and inhibiting degradation (8,60,61). This appears to be mediated by Ras activation secondary to CNIs, but prior immunologic events can also contribute. Treatment of patients with CAN with ACE inhibitors or ARBs decreases intragraft expression of TGF-β (38,52,62–64). Clinically this is associated with a decrease in proteinuria. This effect is independent of BP control, as other classes of antihypertensive drugs

have had no effect on expression of TGF-β (48). Moreover, there is evidence that early treatment with ACE inhibitors or ARBs before established CAN prevents its development. Use of ACE inhibitors or ARBs in a rat model of CAN demonstrated better preservation of glomerular and tubulointerstitial structures (65,66). In a study of 16 kidney transplant recipients with well-preserved graft function, urinary TGF-β excretion and the response of plasma renin activity to ACE inhibitors was predictive of future development of CAN (67). This suggests that renal transplant patients may benefit from treatment with the agents early after transplant.

Dyslipidemia

Lipid abnormalities are common after renal transplantation (68). Factors contributing to this problem include renal dysfunction, diabetes, immunosuppressive drugs (steroids, CNIs, rapamycin), and other drugs such as diuretics (69). Dyslipidemia is a well-established risk factor for cardiovascular disease. It may also contribute to the progression of chronic renal failure (70), but it is difficult to sort out whether this effect is independent of hypertension, proteinuria, and diabetes, since these risk factors quite often coexist. Putative mechanisms by which lipids can contribute to progressive renal disease include an increase in oxidative stress, macrophage/monocyte activation, induction of apoptotic factor, and activation of prosclerotic growth factors.

Experimental evidence shows a benefit from the use of statins on these proposed adverse mechanisms apart from the lipid lowering effect. While there is some evidence that the use of statins in patients with CKD can slow the progression of renal failure (71,72), the beneficial effect on cardiovascular events is more compelling (73–75). Used in transplantation, there may be some immunologic benefit. The use of statins in heart transplant patients was shown to reduce the risk of development of chronic rejection or "transplant coronary artery disease" (76) as well as decreasing the frequency of acute rejection. A small study of statins in renal transplant patients showed a reduction in the incidence of acute rejection (77), but this finding has not been confirmed in other studies (78,79). The use of statins with or without other antilipemic agents in renal transplant patients is safe and effectively improves lipid abnormalities (80,81). There is an interaction between the metabolism of CNIs and statins (82,83). This can lead to significantly higher blood levels of one or both drugs, which can lead to toxicity (84,85). There have been case reports of rhabdomyolysis occurring with the combined use of statins and CNIs (86), but overall the incidence of this complication appears to be low.

Several studies using animal models show benefits with the use of statins that potentially could have a positive impact on the progression of CAN in humans, including antiproliferative (87), anti-inflammatory (88), and vasodilatory effects (89). Despite these findings, evidence supporting the use of statins to prevent progression of CAN is mixed (90). The recent Assessment of Lescol in Renal Transplant trial (ALERT) (80) failed to show a beneficial effect on graft loss or doubling of serum creatinine despite significant improvement in lipids and decreased cardiac deaths and nonfatal myocardial infarctions. What seems more clear is that the use of statins to improve lipid abnormalities in this group of patients can improve survival and reduce cardiovascular morbidity (91–93).

Oxidative Stress

Chronic kidney disease is associated with increased oxidative stress. Oxidative stress may contribute to the progression of chronic renal failure by up-regulation of proinflammatory cytokines leading to an increase in interstitial inflammation (94). Oxidative stress may also play a role in the higher risk of CV events seen in these patients (95).

An increase in oxidative stress has also been demonstrated in kidney transplant patients with renal dysfunction due to CAN, although this can also be present with well-preserved graft function (96,97). The use of CNIs in renal transplant recipients appears to contribute to the higher oxidative stress seen with CAN than that seen in patients with CKD. Animal studies have shown a beneficial effect on markers of oxidative state with the use of antioxidants such as vitamin E, vitamin C, and n-acetylcysteine (98). A reversal of histologic changes comparable to CAN seen in a rat model was also demonstrated with the use of these agents.

Whether the use these agents results in improved clinical outcome in the renal transplant population has not been well studied. There are a few studies that suggest that the use of antioxidants may be useful in renal transplant patients. In one study, administration of vitamin C was shown to improve endothelium-dependent dilation in renal transplant patients (99); in another, treatment of hyperhomocysteinemia with folic acid improved total antioxidant capacity (100). In a retrospective study, kidney transplant patients with CAN who had received 1,25-dihydroxyvitamin D_3, compared with those who had not, had better graft survival (101). Whether targeted antioxidant therapy is indicated in transplant patients to prevent or slow progression of CAN or reduce cardiovascular risk that may be associated with higher oxidative state deserves further study.

Use of Aspirin

The use of low-dose aspirin has been shown to prevent primary and secondary complications of cardiovascular disease via its effect on inhibiting platelet function and progression of atherogenesis. Renal transplant recipients, in addition to chronic renal failure, often have other risk factors for cardiovascular disease such as hypertension, diabetes, and dyslipidemia, or may already have documented coronary artery disease or prior cardiovascular events, and aspirin therapy may be indicated for these reasons. Progressive renal graft impairment in CAN is associated with a transplant vasculopathy of varying degrees and contributes to ischemic injury to the graft. There is preliminary evidence that the addition of low-dose

aspirin to the medical treatment regimen of a transplant recipient can improve long-term allograft survival (102).

Other Medical Complications of the Failing Transplant

Renal transplant patients with failing allografts will often have the same complications associated with CKD. Anemia and electrolyte abnormalities (hypocalcemia, hyperkalemia, acidemia) often appear earlier than expected for the degree of renal function in those with CAN compared to native kidney disease (103,104). Gout may be prominent early in the course of renal decline. The onset of hypermagnesemia, however, may be delayed compared to other etiologies of CKD, as CNIs can be associated with hypomagnesemia (105,106). The exact reason for this is controversial, with some data supporting and other refuting an increase in urinary magnesium excretion (107).

Hyperkalemia, anemia, and acidemia are associated with the prominent interstitial fibrosis displayed in CAN. Hyperkalemia and acidemia are also influenced by down-regulation of aldosterone receptor levels and decreased distal tubular response to mineralocorticoids due to CNI use (104,108–112). Kayexalate may be very helpful in lowering potassium levels. Kayexalate dosing schedules will vary (e.g., 15–60 g/day, every other day to weekly) according to food intake and other medication needs (β-blockers, ACE inhibitors, angiotensin II receptor blocker inhibitors, furosemide, hydrochlorothiazide, fludrocortisone). Given the comparison of kidney transplants to "remnant nephropathy" and the inhibition of cyclosporine-induced interstitial fibrosis and arteriolopathy with spironolactone in animal models (113,114), there may be theoretical concern about promoting renal fibrosis with the use of mineralocorticoids for treatment of hyperkalemia.

Anemia

Anemia is exacerbated in recipients of poorly functioning allografts by treatment with immunosuppressive medications that impair red cell production such as azathioprine, MMF, and sirolimus (10,115–117). The use of ACE inhibitors and ARBs can cause anemia, possibly by inhibiting growth of erythroid precursors (118). Infection with parvovirus B19 has been reported to cause anemia in renal transplant patients; the anemia will often be corrected with a decrease in immunosuppression and administration of IVIg (119,120).

Erythropoietin (EPO) should be started when patients meet the criteria established for treatment of anemia in CKD. The optimal hemoglobin level in the setting of a failing allograft has not been established, but a reasonable target is 11–12 mg/dl, as recommended by the K/DOQI guidelines (121). Adequate treatment of anemia in renal transplant recipients can improve quality of life (103,122), improve left ventricular architecture (123), and potentially improve survival by reducing the incidence of cardiovascular events (124). Correction of anemia using EPO can potentially reduce the need for transfusions. This has significant implications for the patient's status as a candidate for retransplantation, since it may lessen the likelihood of sensitization. Administration of EPO in this setting does not appear to be detrimental to graft function or significantly worsen BP control.

Correction of anemia with EPO has been suggested to retard the progression of renal failure in CKD (125). EPO may be cytoprotective if administered prior to injury (such as ischemia with transplantation) and there are nonrandomized treatment data to support a slowing of renal decline in some allograft recipients with EPO administration. However, there are no randomized prospective data supporting a protective effect of EPO on allograft function when given after transplant (4,126–128). The result of a randomized trial in France evaluating the impact of EPO on progression of renal failure in renal allograft recipients is awaited.

Diabetes

Diabetes mellitus is one of the common etiologies of end-stage renal disease (ESRD) in patients presenting for renal transplantation. In addition, use of corticosteroids and CNIs for immunosuppression can be associated with the development of diabetes after transplantation. New onset diabetes develops on average in 20% of transplant recipients by 3 years after transplant (129). Both new onset and preexisting diabetes are associated with decreased graft survival due to development of diabetic nephropathy. Glycemic control has not yet been shown to prolong survival in those developing posttransplant diabetes. However, a biopsy study showed that intensive treatment in type 1 diabetic recipients of renal transplants resulted in less mesangial expansion, arteriolar hyalinosis, and glomerular basement membrane thickening than conventional treatment (130). In addition, there is evidence that infections are more common with poor glycemic control (131,132). Glucose control should be optimized in all recipients.

Obesity

Obesity is becoming more common in patients as they present for kidney transplantation (133), a phenomenon that parallels the general population. Obesity may be a risk factor for development of CKD or more rapid progression of renal failure in already established disease (134). Hypertension, dyslipidemia, or diabetes associated with obesity may play a greater role. These factors certainly add to the patient's risk of cardiovascular events, which is a major cause of death after transplantation. Although there is disagreement, the majority of evidence at the present time does not show a significant decrement of kidney graft survival or progression of CAN in obese patients compared to nonobese patients (135–137). However, obesity has been shown to increase the risk of posttransplant diabetes mellitus (138,139), particularly in those patients who continue to gain weight after transplantation.

While obesity in and of itself has not been clearly shown to increase the rate of kidney graft loss, it puts the patient at risk for a constellation of coexisting adverse risk factors for renal allograft and patient survival (140,141). The use of corticosteroids may contribute to weight gain after transplantation. However, the evidence is not

convincing that steroid withdrawal beyond 5 mg/day results in a significant benefit in terms of weight loss or improvement in metabolic abnormalities (142–145), and late steroid withdrawal may precipitate acute rejection or result in a decrease in long-term graft survival (142,144). Intensive dietary intervention may be helpful in achieving weight loss or minimizing weight gain after kidney transplantation in obese patients (146,147). Gastric bypass has been used in a small number of patients with some success (148,149).

Stopping Immunosuppression

Once the allograft has failed, the question is when and how to safely stop immunosuppressive agents. The goal is to stop the drugs without resulting in symptomatic rejection or drug withdrawal side effects. The obvious advantages of stopping immunosuppression are the avoidance of infection, malignancy, and the metabolic side effects associated with their use. Infections, infectious death, and cardiovascular death are increased in those with failed allografts maintained on immunosuppressive agents (150). In those with multiple cutaneous carcinomas, stopping immunosuppression may help to halt tumor development (151,152).

There are many ways to discontinue immunosuppressant medications. The rapidity of immunosuppression withdrawal is program and patient dependent. Some programs abruptly stop MMF or azathioprine, wait for 3–4 weeks, stop the cyclosporine or tacrolimus, wait another 3–4 weeks, then taper the steroids by 2.5 mg/day each month. The steroid taper for some programs is by 1–2 mg every 1–2 months. Some programs taper the CNIs after stopping the antimetabolite. During withdrawal, patients will occasionally develop acute rejection, as manifested by asymptomatic hematuria or acute allograft swelling, fever, and pain that necessitates nephrectomy. For some patients, development of painful arthralgias is the rate limiting side effect. If allograft symptoms develop but are not too severe, most transplant programs treat by increasing oral steroids again to about 40–60 mg/day for a few days and then proceeding with a slower taper. Overall, most programs stop the antimetabolite drug (MMF, azathioprine), either stop or taper the CNI or sirolimus, and slowly taper the steroids over several months. In those on a steroid-free protocol, the CNI, MMF, or sirolimus is usually tapered over a period of months.

Depression

Patients with CKD are depressed. This is amplified in those with a failing transplant, as they remember the time on dialysis and deal with the grief of losing an allograft. To help counter this depression, exercise and antidepressant medications should be offered. Exercise promotes physical fitness, diminishing the physical retreat noted with the progression of renal disease (153). Likewise, group or individual psychotherapy may provide benefit (154). Those with established social support have less depression than those without and thus greater vigilance for those without social support is needed (155). Antidepressant treatment has not been well studied in the transplant population; both P-450 metabolism as well as renal insufficiency need to be taken into consideration when selecting an agent (156) (Table 3). Citalopram, fluoxetine, and paroxetine are likely safe, but review with the transplant pharmacist before prescribing is wise, as there are often many other medication interactions as well as liver function to consider (157,158). St. John's wort should, however, be avoided, as it induces the metabolism of CNIs and may result in acute rejection (159–161).

Retransplantation

The final issue in caring for the patient with a failing allograft is rereferral for transplantation. This should be done as soon as possible, when the allograft GFR is between 25 cc/min and 30 cc/min, in order to have the patient ready for listing when the GFR reaches 20 cc/min. The time to retransplantation will likely be longer due to the development of anti-HLA antibodies, making it more difficult for the patient to find a compatible organ. Furthermore, discussion about living donor transplantation is important, as living donor transplantation will provide an improved quality of life and survival.

Conclusion

Renal graft failure due to CAN involves numerous factors, both immunologic and nonimmunologic. Medical therapy to prevent CAN or slow the progression to renal failure once it is already established may involve changes in immunosuppressive drug therapy as well as targeted treatment of nonimmunologic risk factors including hypertension, dyslipidemia, antioxidants, and diabetes. Many of the lessons learned in optimizing the care of CKD patients can be applied to those patients with a failing allograft. In some aspects of care in this setting, for example, the treatment of hypertension, there may be more evidence to support specific goals or therapy than for other aspects such as antioxidants. However, the most benefit may be gained by using a multidrug approach to target more than one putative determinant of graft loss (162). This review has emphasized the mechanisms and treatment of allograft dysfunction.

CKD imparts a higher risk of morbidity and mortality due to cardiovascular events, a risk carried with the patient, at least in part, after transplantation. Death with a functioning graft is the most common cause of kidney transplant failure. Most of the mortality after transplantation is due to cardiovascular events. Renal transplant recipients should have aggressive risk factor modification. Many of the interventions discussed above with reference to preserving renal graft function (i.e., treatment of hypertension and hyperlipidemia) are indicated for this reason as well. Transplant patients with failing allografts may require reassessment of their long-term immunosuppressive regimens to avoid or reduce the impact of complications of long-term immunosuppression,

such as cancer. Those patients who eventually reach ESRD are candidates for another kidney transplant, however, they may be highly sensitized and this may negatively impact wait times or the ability to find a suitable living donor.

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