Outcomes in Kidney Transplantation

By Arjang Djamali, Nalinee Premasathian, and John D. Pirsch

It is estimated that there are greater than 100,000 kidney transplant recipients with a functioning graft in the United States. Recent advances in immunosuppression have improved short-term graft survival rates and decreased early mortality by decreasing the incidence and therapy for acute rejection episodes. For those accepted on the waiting list, transplant prolongs patient survival compared with remaining on dialysis. During the 1990s, 3 new immunosuppressive drugs were introduced in clinical kidney transplantation. All were approved for use by the Food and Drug Administration after large, controlled, randomized trials. Mycophenolate mofetil (MMF), when combined with cyclosporine (CSA) and prednisone, lowered acute rejection rates by nearly 50% compared with control. Tacrolimus compared with CSA also significantly reduced acute rejection rates in kidney transplant recipients, but was associated with a significant increase in posttransplant diabetes mellitus (PTDM) in the early trials. When evaluated in combination with MMF, the incidence of PTDM was much lower. At the end of the decade, sirolimus was shown in several randomized trials to lower acute rejection rates and is believed to be less nephrotoxic compared with calcineurin inhibitors. All of the randomized trials were not statistically powered to assess long-term superiority. Registry analyses have been performed that appear to show some long-term benefit of immunosuppressive therapy with MMF. Other outcome assessments in kidney transplant recipients include risk factors for chronic allograft nephropathy, hypertension, hyperlipidemia, and bone disease. Although there are few randomized trials, understanding of the significance of these common complications has progressed and strategies for therapy and intervention have been developed. This article focuses on the randomized trials of immunosuppressive therapy and complications associated with use of these drugs. In addition, we review the current management and intervention for the comorbidities associated with the long-term clinical management of the kidney transplant recipient.

RENAL TRANSPLANTATION is the treatment of choice for end-stage renal disease (ESRD).[1] Short- and long-term graft and patient survival rates have improved significantly during the past decade.[2] Currently, the 5- and 10-year graft survival rates for cadaver donor transplants are 61.3% and 35.8%, respectively. The corresponding patient survival rates at 5 and 10 years are 81.3% and 62.2%, respectively.[3] Because transplant recipients are living longer, chronic long-term management of the transplant patient has grown in importance.

The main causes of kidney transplant failure after the first year are chronic allograft nephropathy (CAN), patient death with a functioning graft, recurrence of original renal disease, and noncompliance (Fig 1). Thus, it is important to assess the long-term risk profile of a kidney transplant recipient seen for the first time in the office. A number of immune and nonimmune mechanisms predict long-term graft and patient outcomes (Fig 1).[4,5] This article focuses on the impact of immunosuppression and important nonimmune mechanisms on long-term patient and graft survival. We primarily considered data extracted from randomized controlled trials, major registries (UNOS, OPTN, SRTR, and the US Renal Data System), meta-analyses, and original landmark reports.

Departments of Medicine and Surgery, University of Wisconsin Medical School, Madison, WI.

Address reprint requests to John D. Pirsch, MD, Department of Surgery, University of Wisconsin Hospital, H4/772 Clinical Science Center–7375, 600 Highland Ave, Madison, WI 53792. Email: pirsch@tx.surgery.wisc.edu

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THE IMPACT OF IMMUNOSUPPRESSION ON LONG-TERM PATIENT AND GRAFT SURVIVAL

Azathioprine

Azathioprine (AZA) combined with corticosteroids was the mainstay of immunosuppression until the introduction of cyclosporine (CSA) in the 1980s. AZA then became part of a triple drug regimen of AZA, CSA, and corticosteroids until the mid-1990s when 3 large randomized trials showed the superior efficacy of mycophenolate mofetil (MMF) over AZA for the prevention of acute rejection after renal transplantation.[6-9] Most centers abandoned the use of AZA with the introduction of MMF.

Mycophenolate Mofetil

Mycophenolate mofetil is a prodrug. It is hydrolyzed rapidly in the stomach and small intestine into the active drug mycophenolic acid (MPA). MPA is a noncompetitive, selective, and reversible inhibitor of inosine monophosphate dehydroge-

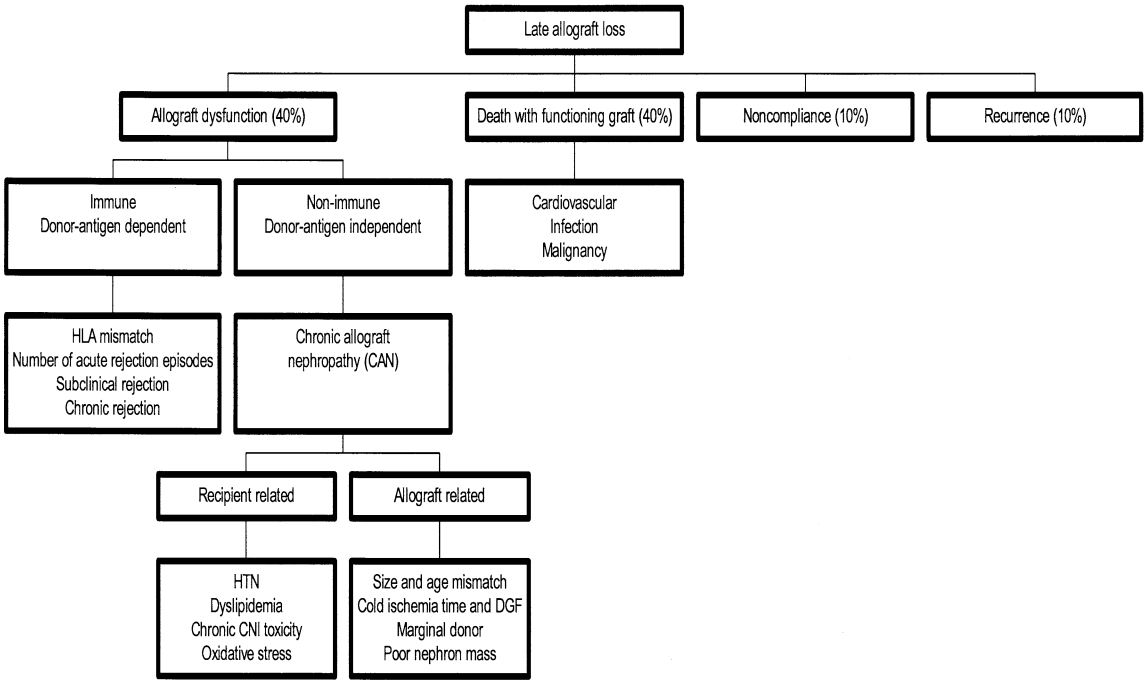

Fig 1. Causes of late allograft loss in renal transplantation.

nase, an enzyme in the de novo synthesis of purine synthesis. The result is: (1) selective, reversible inhibition of T- and B-lymphocyte replication and proliferation; (2) inhibition of the glycosylation of adhesion molecules; (3) inhibition of allospecific antibody production; and (4) modified/inhibited production of cytokines.

MPA undergoes glucuronidation to a stable phenolic glucuronide (MPAG), which is not pharmacologically active.

There are no recommended adjustments for liver or kidney impairment, but patients with renal insufficiency may have higher levels of MPA and more gastrointestinal side effects and bone marrow suppression. Hemodialysis appears to have no major effect on plasma MPA.[10] Peak MPA levels are lower in patients on CSA compared with patients on tacrolimus. This often necessitates a reduction in MMF drug doses in patients on tacrolimus or on prednisone therapy without a calcineurin inhibitor.

Clearly, the short-term benefit of MMF therapy leads to a reduction in acute rejection episodes. The long-term benefit of MMF therapy is less clear (Table 1). The early reduction in acute rejection episodes with MMF did not translate into improved 3-year graft survival in the pivotal studies.[6-9] It is important to note that the studies were not designed or statistically powered to show improved long-term patient and graft survival.

Registry data appears to show a long-term beneficial effect of MMF therapy. A recent analysis of the US Renal Data System registry of 66,774 kidney transplant recipients showed a 27% decrease in chronic allograft failure if treated with MMF at the time of transplant.[11] A subsequent analysis showed that patients who remained on MMF for at least 1 year after transplantation had a decreased incidence and risk for late acute rejection episodes by 65% compared with patients who remained on AZA.[12] The percentage of patients who reached a serum creatinine level of more than 1.8 at 3 years posttransplantation was significantly lower in the MMF group (6%) than the AZA group (13%).[13] The benefit of MMF also extended to African-American transplant recipients with a significant increase in patient and graft survival if treated with MMF in the postoperative period.[14] Currently, MMF is one of the main components of standard triple therapy consisting of calcineurin inhibitors and corticosteroids in most US kidney transplant programs.

Table 1. Results of Randomized, Controlled Trials of MMF Combined With Corticosteroids and Cyclosporine

Result	Result % of Patients (n)		
	AZA/Placebo	MMF 2 g/d	MMF 3 g/d
Biopsy examination–proven rejection at 6 mo			
U.S. registry data*	38.0 (166)	19.8 (167)	17.5 (166)
European†	46.7 (166)	17.0 (165)	13.8 (160)
Tricontinental‡	35.5 (166)	19.7 (173)	15.9 (164)
Graft lost at 6 mo/3 y			
U.S. registry data	8.6/17.1	1.8/13.4	6.7/17.0
European	9.0/16.0	4.2/8.7	6.3/12.8
Tricontinental	3.0/15.4	4.0/14.6	1.8/8.5

NOTE. Concomitant therapy/*P* value:

* AZA, CSA, prednisone and ATGAM/AZA versus MMF 2 g ($P = .0015$); AZA versus MMF 3 g ($P = .0021$)

† Placebo, CSA, and prednisone/both MMF groups versus placebo ($P < .001$)

‡ AZA, CSA, and prednisone/AZA versus MMF 2 g ($P = .0287$); AZA versus MMF 3 g ($P = .0045$)

Data from the Tricontinental Mycophenolate Mofetil Renal Transplantation Study Group,[6] Sollinger,[8] and the European Mycophenolate Mofetil Cooperative Study Group.[9]

Withdrawal of Chronic Immunosuppression

The reduction of immunosuppression to alleviate side effects and decrease long-term complications has been a goal of transplant physicians for decades. However, the consequences of inadequate immunosuppression may lead to transplant failure. In a recent meta-analysis of CSA withdrawal trials, Kasiske et al[15] found no significant difference on graft failure after withdrawal. In contrast, prednisone withdrawal was associated with an increased incidence of acute rejection episodes and some increased risk for graft failure. Two recent randomized trials have addressed the withdrawal of corticosteroids and calcineurin inhibitors.[16,17]

Steroid Withdrawal

A recent multicenter trial evaluated the safety and efficacy of steroid withdrawal in stable, low-risk kidney transplant recipients receiving MMF, steroids, and CSA.[16] The study was double-blinded and controlled. At 3 months, patients were randomized to steroid withdrawal over 8 weeks or maintenance steroid therapy. The study was stopped after 266 patients were enrolled owing to an excess of rejection in the withdrawal group (30.8% versus 9.8%, $P = .0007$). The risk was significantly greater in black recipients (39.6% versus 16% non-black, $P < .001$). There was no short-term difference in patient and graft survival.

Because of the poor results of steroid withdrawal, some centers now practice steroid avoidance or very early withdrawal.[18] This usually is accomplished by using induction therapy with antilymphocyte globulin. The short-term reports have shown excellent results, but long-term data is lacking.

Calcineurin Withdrawal

A recent multicenter trial in Europe, Australia, and Canada randomized patients without severe rejection and serum creatinine levels of less than 400 μmol/L (1.84 mg/dL) at 3 months after renal transplant to remain on sirolimus, CSA, and steroids (N = 215) or to have CSA (Neoral, Novartis, East Hanover, NJ) (N = 215) withdrawn and therapy continued with sirolimus and steroids.[17] The sirolimus level was increased significantly in patients withdrawn from CSA. At 12 months, there was no difference in graft survival (95.8% versus 97.2%, sirolimus-CSA-steroids versus sirolimus and steroids) or patient survival (97.2% versus 98.1%). Acute rejection rates were higher in the sirolimus-steroids group (9.8% versus 4.2%). However, calculated glomerular filtration rate was higher in the sirolimus-steroids group (63 versus 57 mL/min) and blood pressure significantly improved when CSA was withdrawn.[17] This study showed the feasibility of the withdrawal of CSA, but required a significant increase in sirolimus blood levels. The long-term efficacy of this approach is not established.

Table 2. Randomized Studies of Tacrolimus Compared with Cyclosporine-Treated Cadaveric Kidney Transplant Recipients

				% of Patients		
Study	Concomitant Therapy	Study Drug	Number Enrolled	1-y Biopsy Examination–Proven Rejection	Steroid-Resistant Rejection	1-year Graft Survival
Mayer et al[22]	AZA	Tacrolimus	303	17.5*	10.2†	82.5‡
	Steroids	Sandimmune	145	35.9	20.7	86.2
Pirsch et al[23]	AZA	Tacrolimus	205	30.7§	10.7*	91.1‖
	Steroids OKT3/ATGAM	Sandimmune	207	46.3	25.1	87.9

* $P = .001$.
† $P = .004$.
‡ $P = .380$.
§ $P = .001$.
‖ $P = .289$.

C2 Monitoring

CSA has been monitored by using the 12-hour trough level (C0) with relative success in the past 2 decades. However, data have shown that this technique does not always correlate with area under the curve or drug exposure, particularly in poor absorbers of CSA. The new microemulsion formulation of cyclosporine, Neoral, offers more complete and reliable absorption from the gastrointestinal tract than Sandimmune (Novartis). Recent studies showed that measuring the CSA blood level at 2 hours (C2) correlated better with the area under the curve compared with C0. Data suggest that maintaining a C2 level at 1,500 to 2,000 ng/mL for the first month is associated with an improved outcome. A C2 level of approximately 800 ng/mL at 1 year may be associated with improved long-term outcome and less nephrotoxicity. In practical terms, it may be difficult to measure C2 blood levels owing to the timing of blood draws and the necessity for the patient to take CSA 2 hours before the blood draw.[19,20]

Tacrolimus

The mechanism of action of tacrolimus is similar to that of CSA, even though their chemical structures differ greatly. Tacrolimus binds cytoplasmic FK-binding proteins, whereas CSA binds to cyclophilins. Both result in inhibition of interleukin-2 transcription and T-cell activation. The potency of tacrolimus is 10 to 100 times greater than CSA, and the dosages on a mg/kg basis are correspondingly lower than those of CSA. The metabolism of CSA and tacrolimus is similar and primarily eliminated from the body by the cytochrome P-450 3A4 in the liver. Drugs known to alter CSA concentrations are likely to alter tacrolimus concentrations.[21]

Two recent randomized, multicenter studies showed that tacrolimus is more effective than CSA in preventing acute rejection in cadaveric renal allograft recipients (Table 2).[22,23] The incidence and histologic severity of biopsy examination–confirmed acute rejection in the first year was significantly lower in tacrolimus-treated patients compared with CSA-treated patients. The 5-year follow-up evaluation showed equivalent patient and graft survival rates for tacrolimus- versus CSA-treated patients.[24] However, when cross-over to the other treatment arm was counted as graft failure, there was significantly better survival in the tacrolimus-treatment arm. Most of the benefit was seen in African-American recipients who had statistically better long-term graft survival if treated with tacrolimus. There were important differences in the overall incidence of hypertension and hyperlipidemia between the 2 groups. Both common side effects were much lower in tacrolimus-treated recipients.

At 1 year in the US trial, the incidence of new posttransplant diabetes mellitus (PTDM) requiring insulin in tacrolimus-treated patients (19.9%) was significantly greater compared with CSA-treated patients (4.0%).[23] In a multivariate analysis, the development of PTDM was related to race (African Americans having a much higher incidence),

Table 3. Rejection and PTDM in Randomized Controlled Studies of MMF Combined With Tacrolimus in Kidney Transplant Recipients

	Overall Rejection Rates		
Miller et al[25]	TAC + AZA (n = 59)	TAC + MMF 1 g/d (n = 59)	TAC + MMF 2 g/d (n = 58)
12 mo	32.2%	32.2%	8.6%*
Squifflet et al[26]	TAC without MMF (n = 82)	TAC + MMF 1 g/d (n = 79)	TAC + MMF 2 g/d (n = 71)
Biopsy AR	35.4%	15.2%	4.6%†
Ahsan et al[27]	TAC + MMF 2 g/d (n = 72)	CSA + MMF 2 g/d (n = 75)	TAC + AZA (n = 76)
Biopsy AR-2 y	16.7%	22.7%	18.4%‡

	Incidence of PTDM			
	TAC + AZA or No AZA	TAC + MMF 1 g/d	TAC + MMF 2 g/d	CSA + MMF 2 g/d
Miller et al[25]	19%	12.2%	4.7%	—
Squifflet et al[26]	6.1%	10.1%	5.6%	—
Ahsan et al[27]	7.0%	—	8.7%	6.5%

Abbreviation: TAC, tacrolimus.
* $P < .01$ MMF 2 g/d versus MMF 1 g/d or AZA.
† $P = .007$ MMF 2 g/d >MMF 1 g/d > no MMF.
‡ No significant differences across treatment groups.

higher trough levels of tacrolimus, and total steroid dose. At 5-years posttransplant, 41.2% of the PTDM patients on tacrolimus were off insulin.[24] The prevalence of new cases of PTDM requiring insulin after 1 year was 2.6% in the tacrolimus group and 0.7% in the CSA group.

The combination of MMF and tacrolimus has been studied in 3 randomized trials.[25-27] In 2 studies, tacrolimus was used as baseline calcineurin therapy and randomization was to 3 different groups.[25,26] In the United States, the 3 groups were AZA, MMF 1 g/d, and MMF 2 g/d.[25] In Europe, the 3 groups were similar to the US study; however, AZA was not used.[26] All of these patients also received corticosteroids. The third study was a randomized trial comparing tacrolimus and CSA in combination with MMF.[27] There were 3 randomized arms in this study: tacrolimus plus MMF 2 g/d, CSA plus MMF 2 g/d, and tacrolimus plus AZA. These patients all received corticosteroids. The overall rejection rates for the 3 studies are shown in Table 3. All 3 studies showed excellent efficacy with the combination of tacrolimus and MMF. In the US study, the best efficacy was seen with the tacrolimus and MMF 2 g/d group. In the European study, there was a significant difference in acute rejection with either MMF 1 g/d or MMF 2 g/d compared with no MMF. Both groups treated with MMF had substantially reduced rejection episodes. In the 3-arm study with CSA and MMF, there were no statistically significant differences in the incidence of biopsy examination–confirmed acute rejection episodes across treatment groups.[27]

There has been concern about the toxicity associated with the use of MMF and tacrolimus. The first issue is enhanced toxicity from MMF because the MPA levels are higher on the 2 g/d dose, which may lead to more side effects. In all 3 studies, there was a reduction in the MMF doses in the 2 g/d group. In the US study, the average dose for this group at 1 year was 1.5 g/d.[25] In the European study, the average dose was 1.5 g/d at 6 months.[26] In the comparative study of tacrolimus and CSA, the average MMF dose at 2 years was 1.75 g/d.[27] Most of the reduction in MMF dose was owing to gastrointestinal toxicity or leukopenia.

The second issue of concern is the incidence of PTDM with the use of tacrolimus. The relative incidence of PTDM for the 3 studies is shown in Table 3. The results of these studies showed a lower overall incidence of PTDM with the combination of MMF and tacrolimus compared with the US multicenter, randomized study comparing tacrolimus and CSA.

Sirolimus

Sirolimus (rapamycin, Rapamune, Wyeth-Ayerst, Madison, NJ) inhibits cytokine-induced signal

Table 4. Randomized Controlled Trials of Sirolimus in Kidney Transplant Recipients

				% of Patients				
Study	Concomitant Therapy	Study Drugs	Number Enrolled	6 mo ACR	12 mo ACR	12 mo Graft Survival	GFR (mL/min) at 6 mo	
MacDonald AS[28]	CSA	Placebo	130	36.9		87.7*	62.58	
	Prednisone	Sirolimus 2 mg	227	21.1†		90.0	59.07	
	No induction	Sirolimus 5 mg	219	16.0‡		90.9	(3 mo) 56.42	
Kahan BD[29]	CSA	AZA	161	29.8	31.1	94.4	68.78	67.51 (1 y)
	No induction	Sirolimus 2 mg	284	16.9§	21.8	94.3‖	62.29	61.95
	Prednisone	Sirolimus 5 mg	274	12¶	14.6	92.7¶	59.15	55.48

Abbreviations: CR, acute chronic rejection; GFR, glomerular filtration rate.
† $P = .335$.
‡ $P = .056$.
* $P = .366$.
§ $P = .002$.
¶ $P < .001$,
‖ $P = .046$.

transduction pathways and impairs progression through the G1 phase of the cell cycle resulting in inhibition of T-cell activation. Sirolimus has been shown to reduce the incidence of acute renal allograft rejection compared with a control regimen of CSA and steroids (Table 4).[28,29] Replacing AZA with sirolimus in conventional CSA, AZA, and prednisone resulted in a significant decrease in acute rejection at 6 and 12 months.[29] In both of these trials, however, there was a mild decrease in renal function and increased incidence of infection in the sirolimus-CSA arms. Sirolimus also was associated with greater incidences of hyperlipidemia, leukopenia, and wound complications.

Although sirolimus is Food and Drug Administration approved for use with CSA, other immunosuppressive regimens have been used. The combination of tacrolimus and sirolimus appears to be efficacious and is used exclusively for successful islet transplantation.[30,31] The combination of MMF and sirolimus without calcineurin-inhibitors warrants further study because nephrotoxicity can be avoided.[32]

Conclusions

All of the immunosuppressive regimens have significant toxicities. CSA and tacrolimus cause nephrotoxicity and contribute to CAN. Sirolimus is not inherently nephrotoxic, but as an antiproliferative agent can significantly impair wound healing. MMF causes bone marrow suppression and gastrointestinal toxicity. Steroids, CSA, and sirolimus increase lipid levels. Tacrolimus causes a higher incidence of PTDM. The drug selection for given patients should be tailored to provide the maximum efficacy and the least toxicity without jeopardizing the transplant. Drug withdrawal should be performed only when the risk-benefit warrants or in carefully randomized trials because the long-term outcome of drug withdrawal is uncertain.

THE IMPACT OF NONIMMUNE MECHANISMS ON PATIENT AND GRAFT SURVIVAL

Kidney Function

The diagnosis of CAN usually is suggested by slowly increasing plasma creatinine concentration, increasing proteinuria, and worsening hypertension.[33] Hariharan et al[34] recently showed that the most important predictor of graft outcome in kidney transplantation is the 1-year serum creatinine (Scr) level. In a retrospective analysis of 105,742 kidney transplant recipients, the investigators showed that patients with a 1-year Scr greater than 1.5 mg/dL or a change in creatinine level from 6 to 12 months of 0.3 mg/dL or greater had a significant decrease in the projected median graft half-life. That is, a progressive cadaver graft half-life drop from 13.2 to 5.1 years as the 1-year Scr increased from 1.5 to 3 mg/dL. It seems that regardless of the type of kidney injury (immune or nonimmune) during the first year posttransplant, it is the 1-year Scr level that determines long-term graft outcome.

In addition to Scr, the evaluation of kidney transplant function includes the assessment of proteinuria. Proteinuria in a kidney transplant recipient can be secondary to CAN (50%), recurrent glomerulonephritis (30%), renal vein thrombosis, reflux nephropathy, and drug toxicity,[35] and is an independent risk factor for disease progression.[36]

Cardiovascular Disease

Cardiovascular disease is defined as ischemic heart disease, cerebral vascular disease, or peripheral vascular disease, and is the leading cause of death in kidney transplant recipients.[37] Approximately 23% of kidney transplant recipients develop ischemic heart disease and 15% develop cerebral vascular disease or peripheral vascular disease by 15 years after transplantation.[38] Thus, the National Kidney Foundation Task Force on cardiovascular disease concluded that a number of potentially modifiable risk factors could be targeted for intervention.[39] Although there is currently insufficient evidence to suggest that screening of asymptomatic patients with cardiac stress tests reduces morbidity or mortality rates after renal transplantation, regular screening tests should be considered in kidney transplant recipients who have a history of coronary artery disease.

Hypertension

Hypertension (HTN) is the second leading cause of ESRD in the United States and a major risk factor for cardiovascular disease. The incidence of posttransplant HTN is as high as 80%.[40] The causes of posttransplant HTN include the use of calcineurin inhibitors, prednisone, pre-existing HTN, primary kidney disease, renal transplant artery stenosis, and renal transplant dysfunction. Opelz et al[41] showed that systolic and diastolic HTN were both independent risk factors for graft loss. There are currently no large, randomized, controlled trials showing that lowering blood pressure would improve long-term outcome in kidney transplantation. Furthermore, there is no consensus regarding the optimal choice of drug therapy. However, calcium channel blockers, angiotensin-converting enzyme inhibitors (ACEIs), diuretics, and β blockers constitute the backbone of the pharmacologic treatment in posttransplant HTN.[42] Although randomized controlled trials have used calcium channel blockers and ACEI successfully in the treatment of posttransplant HTN,[43,44] long-term effects of these drugs on graft function remains unknown. It has been shown clearly that ACEIs and angiotensin receptor blockers slow the rate of disease progression in patients with chronic kidney disease (CKD).[45,46] These drugs therefore offer a good therapeutic option for the management of posttransplant HTN in patients without hyperkalemia, unexplained anemia, or renal transplant artery stenosis.[47,48]

Dyslipidemia

Dyslipidemia is an established risk factor for cardiovascular mortality.[38] Posttransplant hyperlipidemia affects 60% to 80% of patients[49] and it can be secondary to the immunosuppressive treatment, particularly sirolimus,[50] corticosteroids, and CSA. Other factors, such as preexisting familial dyslipidemia, obesity, renal dysfunction, proteinuria, diabetes, or tobacco use contribute to posttransplant hyperlipidemia.[51] Kasiske et al[52] recently showed that early posttransplant treatment with HMG-CoA inhibitors did not decrease the incidence of acute rejection. Although there are no randomized controlled trials showing that hyperlipidemia is an independent risk factor for CAN or that its treatment slows the rate of disease progression in kidney transplant recipients, retrospective studies have shown that posttransplant dyslipidemia is a risk factor for long-term graft loss.[53] Cosio et al[54] recently showed that the use of HMG-CoA inhibitors improved the survival of kidney transplant recipients by 24%. Treatment of posttransplant dyslipidemia should be based on National Cholesterol Education Program (NCEP) guidelines.[55] HMG-CoA inhibitors are the treatment of choice; moreover, they have pleiotropic effects[56] that might benefit kidney transplant recipients. However, because of drug interactions, HMG-CoA inhibitor side effects (hepatitis, myositis, and rhabdomyolysis) occur more in kidney transplant recipients who are also on calcineurin inhibitors, fibrates, or nicotinic acid.[51]

Diabetes

Diabetes is the most common cause of ESRD in the United States and PTDM is a common problem in kidney transplantation. The incidence of PTDM is up to 20%.[57] PTDM frequently develops as a result of the immunosuppressive therapy with corticosteroids, CSA, and, particularly, tacrolimus.[23] Diabetes contributes significantly to posttransplant

morbidity and mortality[58,59] and prospective, randomized, controlled trials in patients with CKD have shown that glycemic control,[60] ACEI,[61] and angiotensin receptor blockers[46] delay disease progression in patients with diabetes. Although the diagnosis of PTDM might not present a challenge because it often is made during the first posttransplant year, current knowledge mandates that all kidney transplant recipients with diabetes should be monitored closely for their glycemic control and kidney function. Judicious use of ACEIs or angiotensin receptor blockers as described earlier in the section on HTN also is recommended.

Anemia

The incidence of late posttransplant anemia is about 30% to 40%.[62,63] It may result from inadequate erythropoietin production, iron deficiency, drug-induced myelosuppression, hemolytic and uremic syndrome, and parvovirus B19 infections.[64] Currently, there is insufficient evidence to recommend for or against partial correction of anemia with iron and/or recombinant human erythropoietin for the unique purpose of slowing the rate of decline of glomerular filtration rate in patients with CKD or in kidney transplant recipients. However, anemia has significant morbidity and mortality and is associated with cardiovascular complications in the general population,[65] patients with CKD,[66] and kidney transplant recipients,[67] and its treatment may improve outcome.

Osteoporosis

Posttransplant osteoporosis occurs in up to 60% of kidney transplant recipients.[38] Osteoporosis is defined by a T score of -2.5 or less based on dual energy radiograph absorptiometry scan of the lumbar spine and the dominant hip. Posttransplant bone loss may cause pain and fractures, and is predominantly a consequence of treatment with corticosteroids and calcineurin inhibitors, previous renal osteodystrophy, hyperparathyroidism, metabolic acidosis, and smoking.[68] Although the maximum bone loss occurs within the first 3 to 6 months, it continues during the later stages at a slower rate. Elemental calcium (1–1.5 g/d), vitamin D (400-800 UI/d), and bisphosphonates have been shown in prospective, randomized, controlled trials to delay the rate of posttransplant bone loss.[69,70]

Infections

Most patients have stable allograft function and are on minimal maintenance immunosuppressive therapy 1 year after transplant. Therefore, infection in the majority of these patients is often similar to that seen in the general population. Less than 20% of these patients, however, will have clinically evident symptoms of chronic viral infections. These include cytomegalovirus infections, lymphoproliferative disorders caused by Epstein Barr virus, chronic hepatitis, acquired immune deficiency syndrome, and the more recently described polyomavirus type BK (BK virus).[71,72] The latter is a virus with a high tropism for the genitourinary tract. Polyomavirus-induced nephropathy currently is recognized as an important cause of renal allograft failure and often is manifested by an unexplained increase in serum creatinine level. The diagnosis can be made by renal biopsy examination and urine cytology with identification of characteristic cytopathologic changes, or polymerase chain reaction.[73,74] There is currently no specific antiviral therapy for this infection and the main option is decreasing immunosuppressive medications. About 10% of kidney transplant recipients who have had multiple episodes of rejection and high levels of immunosuppression are at risk for serious opportunistic infections such *Pneumocystis carinii*, *Listeria monocytogenes*, and *Nocardia asteroids* infections.

Malignancies

The use of immunosuppression in kidney transplant recipients increases the long-term risk for malignancy approximately 3 to 5 times that in the general population.[75] These malignancies include particularly skin cancers and non-Hodgkin's lymphomas, and, to a lesser extent, Kaposi's sarcoma, in situ carcinomas of the uterine cervix, carcinomas of the vulva and perineum, renal carcinoma, hepatobiliary carcinomas, and a variety of sarcomas.[75] Risk factors for developing de novo posttransplant malignancies were analyzed recently in a retrospective single-center study[76] and included age, pretransplant splenectomy, invasive cancer, and cigarette smoking. Aggressive screening for early detection of malignancies therefore is warranted in kidney transplant recipients.

Noncompliance

Transplant recipients are required to take immunosuppressive treatment for the rest of their lives. However, compliance is often lower than desired. Chisholm et al[77] reported a compliance rate of only 48% at 1 year posttransplant in a free-of-charge, multidrug immunosuppressive treatment. In a retrospective study by Schweizer et al,[78] 91% of kidney transplant recipients who were noncompliant with medications and follow-up care either lost their grafts or died. This emphasizes the role of primary care physicians in a multidisciplinary approach to kidney transplant recipients' medical and psychosocial needs.

SUMMARY

Nephrologists and primary care physicians are being more involved in the care of kidney transplant recipients. Long-term graft survival depends on long-term patient survival. Similarly, a functioning kidney transplant significantly prolongs life compared with dialysis. Kidney transplant recipients can be considered as a unique group of patients with CKD. Therefore, providers caring for these patients should monitor their kidney function closely and screen and treat risk factors, such as hypertension, diabetes, dyslipidemia, infections, malignancies, anemia, bone disease, and noncompliance. This goal can be achieved through the current recommendations and close collaboration with the transplant center.

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