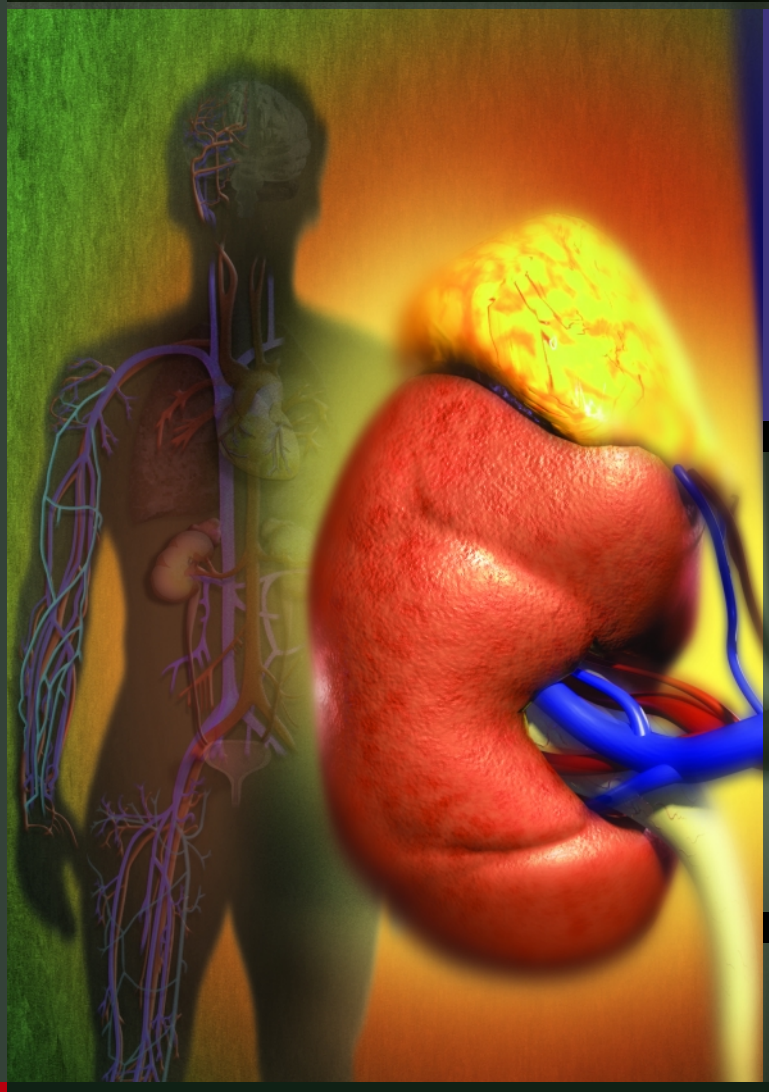
Implications of
PRESERVING LONG-TERM RENAL FUNCTION
After Renal Transplantation

Presented by:

National Institute of Allergy and Infectious Diseases of
the National Institutes of Health
U.S. Department of Health and Human Services

A Case Study Approach to the Clinician's Challenge in Preserving Long-term Renal Function



FIFTH IN A SERIES OF MONOGRAPHS

BASED ON A ROUNDTABLE MEETING

HELD NOVEMBER 11, 2003

IN BETHESDA, MARYLAND

In Cooperation With:

- American Society of Transplant Surgeons
- United Network for Organ Sharing
- North American Transplant Coordinators Organization
- International Transplant Nurses Society

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Transplant surgeons, transplant nephrologists, transplant nurses, transplant coordinators, pharmacists, and other healthcare professionals who are involved in the treatment and management of renal transplant recipients

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Educational Objectives

At the conclusion of this program, the participant will be able to:

- Describe how the challenges in immunosuppressive treatment of kidney transplant recipients have changed in recent years
- Discuss the importance of greater awareness of renal injury as a primary factor in chronic allograft nephropathy and that preserving renal function following transplantation is a treatment priority
- List the various treatment protocols and describe how each offers clinicians viable options for customized treatments
- Discuss how combinations of newer immunosuppressive agents allow for customization of treatment regimens that meet specific patient needs

Term of Approval

Date of Original Release: November 2004

Expiration Date: November 30, 2005

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Stuart M. Flechner, MD, has received grant/research support from Novartis Pharmaceuticals Corporation and Wyeth, has been a consultant for Novartis Pharmaceuticals Corporation, Roche Laboratories Inc, and Wyeth, and has served on the speakers bureau for Novartis Pharmaceuticals Corporation, Roche Laboratories Inc, and Wyeth.

Donald E. Hricik, MD, has received grant/research support from Fujisawa Healthcare, Inc, Novartis Pharmaceuticals Corporation, and Wyeth, and has been a consultant for Fujisawa Healthcare, Inc, Novartis Pharmaceuticals Corporation, and Wyeth.

Bruce Kaplan, MD, has received grant/research support from Novartis Pharmaceuticals Corporation and Roche Laboratories Inc, and has been a consultant for Bristol-Myers Squibb Company, Novartis Pharmaceuticals Corporation, and Roche Laboratories Inc.

Bertram L. Kasiske, MD, has received grant/research support from Bristol-Myers Squibb Company and Merck & Co, Inc, has been a consultant for Wyeth, and has served on the speakers bureau for Fujisawa Healthcare, Inc, Novartis Pharmaceuticals Corporation, Roche Laboratories Inc, and Wyeth.

Marc I. Lorber, MD, has received grant/research support from Novartis Pharmaceuticals Corporation and Wyeth, and has served on the speakers bureau for Novartis Pharmaceuticals Corporation and Wyeth.

Akinlolu O. Ojo, MD, PhD, has received grant/research support from Genentech, Inc, and Wyeth, has been a consultant for Novartis Pharmaceuticals Corporation, and has served on the speakers bureau for AstraZeneca, Merck & Co, Inc, and Pfizer Inc.

Kim Solez, MD, has indicated that he has no financial interest or affiliation to report.

A Case Study Approach to the Clinician's Challenge in Preserving Long-term Renal Function

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Introduction

Challenges in immunosuppressive treatment of kidney transplant recipients have changed in recent years. With the optimization of combination immunosuppressive regimens, acute rejection rates (within 1 year of transplantation) have decreased to less than 20%, and, at some centers, rates of less than 10% are routine.[1] Current procedures allow successful kidney transplantation in a broader range of recipients. Also, the use of expanded donor criteria for determining acceptable risk of graft survival has been facilitated by recent improvements in treatments.[2] Despite these strides, prevention of chronic allograft nephropathy and long-term graft survival remain challenging.[1] In addition, the older mean age of kidney transplant recipients has resulted in the need to manage immunosuppression in the context of multiple, sometimes long-standing comorbidities.[2]

Calcineurin inhibitors (CNIs), cyclosporine and, more recently, tacrolimus, have been the mainstay of immunotherapy. Their use can be credited with much of the remarkable reduction in acute rejection rates over the last 20 years. Ironically, the reduction in acute rejection rates has revealed the significant role of CNI nephrotoxicity in the deterioration of renal function, which can lead ultimately to graft loss. Data from 10 years of follow-up in kidney transplant recipients treated initially with cyclosporine or azathioprine indicate that the graft survival benefit with cyclosporine is no longer significant after 3 years of treatment. This decline is preceded by a progressive decrease in renal function, which may be attributed to the nephrotoxic properties of CNIs that lead to structural damage to the transplanted kidney.[3]

Cardiovascular (CV) effects of calcineurin inhibition, including hypertension and dyslipidemia, may further compromise long-term outcomes.[4,5] In addition, cyclosporine- and tacrolimus-based immunosuppressive protocols have been associated with increased rates of posttransplant diabetes mellitus (PTDM). However, the incidence of PTDM associated with tacrolimus is significantly greater than with cyclosporine or other immunosuppressive therapies.[6]

Fortunately, the introduction of new immunosuppressive drugs with complementary mechanisms of action and different side effect profiles may improve long-term graft and patient survival. Mycophenolate mofetil (MMF) has been available for 10 years and has proven to be superior to azathioprine in preventing rejection episodes when used in combination with cyclosporine.[7,8] The target of rapamycin (TOR) inhibitor sirolimus exhibits immediate benefits similar to those of CNIs with virtually no nephrotoxicity and less chronic allograft nephropathy.[9] Immunosuppressive protocols using sirolimus, everolimus, and MMF have been successful in reducing the dosage of or entirely eliminating CNIs.[10-13] Induction protocols using antithymocyte antibodies and anti-CD25 monoclonal antibodies have increased treatment flexibility and customization of immunosuppressive therapy as well.[14] Nonetheless, studies evaluating CNI-free immunosuppression have had mixed outcomes, and these results need to be evaluated carefully.

Innovative use of these immunosuppressive treatment strategies can be adapted for individual patient needs. Approaches include drug substitution, drug sparing, and drug elimination. This monograph, the fifth in a series, contains four cases illustrating treatment challenges commonly encountered in this new era of kidney transplantation. Treatment plans that address the needs of these individuals are presented along with a discussion of the clinical data supporting the suggested immunosuppressive strategy.

Case 1—John R. (Table 1)

Presentation

John R. presents for routine care posttransplantation. He is a 52-year-old African American who was a self-employed electrician. John has been unable to work for almost 5 years because of poor health. He has a family history of hypertension and cardiovascular disease (CVD).

In his 30s, John developed hypertension, which was a major factor in the development of his end-stage renal disease (ESRD). His first of three coronary angioplasty procedures was performed when John was 45. Angioplasty with stenting was administered when he was 46 and again when he was 49. He developed proteinuria at the age of 44, and, over the next few years, his renal function deteriorated, eventually requiring treatment with hemodialysis for approximately 2 years. He received a deceased-donor kidney transplant from a 56-year-old man 18 months ago.

Two episodes of acute rejection occurred during the first 3 months posttransplantation. The first episode resolved after treatment with pulse methylprednisolone and the second after treatment with OKT3. Since the last episode, John has been maintained with cyclosporine 4 to 5 mg/kg/day (adjusted to trough whole blood level values of 220 ng/mL), MMF (1 g bid), and prednisone (10 mg/day). His hypertension had been controlled (128/78 mm Hg) with metoprolol (100 mg bid) until recently.

Table 1

Case 1. Drug Substitution: Sirolimus Substituted for Cyclosporine

Name: John R. **Age:** 52 years **Race/Ethnicity:** African American

Baseline medications: cyclosporine (4-5 mg/kg/day), MMF (1 g bid), prednisone (10 mg/day), metoprolol (100 mg bid)

Diagnosis: chronic allograft nephropathy

Treatment: switch to sirolimus (whole blood target trough levels of 10-15 ng/mL), MMF (1 g bid), prednisone (10 mg/day), metoprolol (100 mg bid), amlodipine (5 mg qd), atorvastatin (10 mg qd)

	Baseline	Presentation	Follow-up	2nd Follow-up
Time after transplantation (mo)	6	18	24	27
Serum creatinine (mg/dL)	1.6	2.1	1.8	1.8
Urinalysis	3+ protein			
BUN (mg/dL)	32	40	24	Not done
Uric acid (mg/dL)	6.0	7.5	5.6	Not done
BP (mm Hg)	137/85	145/92	132/82	128/78
Lipid parameters (mg/dL)				
Total cholesterol	224	260	307	195
LDL cholesterol	126	130	135	124
HDL cholesterol	38	38	35	40
Triglycerides	230	254	450	228

MMF, mycophenolate mofetil; BUN, blood urea nitrogen; BP, blood pressure; LDL, low-density lipoprotein; HDL, high-density lipoprotein.

Evaluation

John's blood pressure (BP) was 145/92 mm Hg on presentation. His serum creatinine level had increased gradually over the last year from a 6-month baseline of 1.6 mg/dL to 2.1 mg/dL. His urinalysis showed a 3+ protein and no signs of hematuria or infection. Levels of total cholesterol (TC) were 260 mg/dL, low-density lipoprotein cholesterol (LDL-C) 130 mg/dL, and triglycerides (TG) 254 mg/dL. John's high-density lipoprotein cholesterol (HDL-C) level was slightly low at 38 mg/dL.

Diagnosis/Treatment Plan

These findings are consistent with a clinical diagnosis of chronic allograft nephropathy. John was switched from cyclosporine to sirolimus (whole blood sirolimus target trough levels of 10 to 15 ng/mL). His doses of MMF (1 g bid) and prednisone (10 mg/day) remained the same. Amlodipine (5 mg qd) and atorvastatin (10 mg qd) were added.

Follow-up Report

After 6 months on sirolimus (24 months posttransplantation), John returned for evaluation. His serum creatinine values had decreased to 1.8 mg/dL. His BP was 132/82 mg Hg. His lipid levels were elevated (TC 307 mg/dL, LCL-C 135 mg/dL, TG 450 mg/dL); therefore, his atorvastatin dose was increased to 20 mg qd. A checkup 3 months later showed that his lipid profile had stabilized.

Clinical Considerations

John is typical of many kidney transplant recipients for whom the risk of graft rejection must be managed along with high risk of CV events, which are the primary cause of death in kidney transplant recipients, accounting for between 35% and 50% of all mortality in this population.[5] Many factors known to increase CV risk in the general population are common in the transplant population as well. These include hypertension, dyslipidemia, diabetes or metabolic syndrome, and atherosclerosis.[5] A major cause of ESRD in African Americans, hypertension generally occurs at younger ages and results in higher rates of stroke, CVD, and CV death in this population.[15] Although the benefits of modifying these risk factors have not been extensively evaluated in transplant recipients, particularly African American recipients, it is reasonable to expect the benefits can be generalized to this transplant population.

The pathophysiology of CVD is hard to separate from renal dysfunction. Poor renal function (serum creatinine levels >1.5 mg/dL) at 1 year posttransplantation is strongly associated with CV mortality in kidney transplant recipients (Figure 1).[1] Moreover, loss of renal function resulting from acute rejection may be the real culprit in the consistently observed association between acute rejection episodes, chronic allograft nephropathy, and subsequent graft loss. Meier-Kriesche et al have reported that the 6-year graft survival rate for patients with acute rejection who recovered renal function to within 5% of their 6-month baseline serum creatinine value was similar to that of kidney transplant recipients who had no acute rejection episodes at all (72.7% and 74.4%, respectively). The 6-year graft survival rate for individuals who did not recover baseline renal function was only 50.4%, indicating that recovery of renal function is the critical factor influencing long-term graft survival following acute rejection.[16]

Graft survival and acute rejection episodes also correlate with high BP, a common problem in the kidney transplant population.[17] In a study of 1295 individuals who had functioning grafts 1 year after transplantation, more than 50% had at least stage 1 or 2 hypertension (systolic BP ≥140 mm Hg or diastolic BP ≥90 mm Hg), as defined by the Joint National Committee on the Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. This observation was independent of antihypertensive treatment.[17,18] Less than 4% of these patients were normotensive (BP <120/80 mm Hg) without medication.[17]

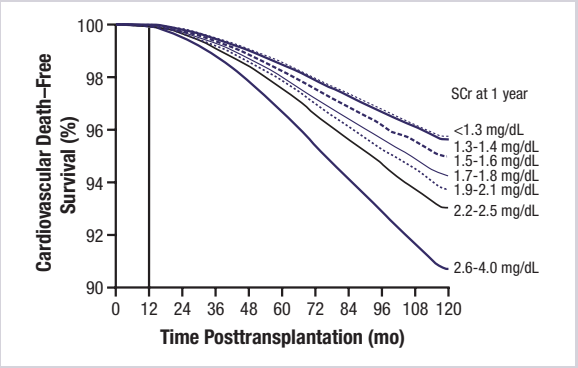
In this same study, systolic BP was associated with graft failure, death-censored graft failure, and death. For individuals with a functioning graft at 1 year posttransplantation, the adjusted relative risk of graft failure was 1.13 (95% confidence interval, 1.09 to 1.17; $P<.0001$) for each 10–mm Hg increase in BP.[17]

Although the use of cyclosporine, the mainstay of immunosuppression, has resulted in a dramatic decline in rates of acute rejection, the significant increase in graft survival does not appear to extend beyond 3 years posttransplantation.[3] Marcen et al found that after 3 years of treatment with cyclosporine, the graft survival rate began to decline and, by 10 years, was statistically similar to rates in patients who had received azathioprine instead of cyclosporine. In the cyclosporine group, 41% of graft loss was attributed to chronic allograft nephropathy compared with 16.8% in the azathioprine group.[3] Ten-year patient survival rates were similar for the two groups (70% for azathioprine and 75% for cyclosporine). Hypertension was more frequent ($P=.017$) and mean arterial pressure was higher in the cyclosporine group than the azathioprine group (110 ± 11 mm Hg and 102 ± 15 mm Hg, respectively; $P=.002$). Hypercholesterolemia was also more common in cyclosporine-treated patients.[3]

The lack of long-term graft survival benefit may be attributed to cyclosporine nephrotoxicity that results in irreversible structural changes and loss of renal function in the transplanted kidney.[19] Furthermore, acute rejection episodes that occur in the setting of cyclosporine-induced nephrotoxicity result in a higher incidence of biopsy-confirmed chronic

Figure 1

Cardiovascular Death–Free Survival by Serum Creatinine (SCr) Levels at 1 Year Posttransplantation



Adapted with permission from Meier-Kriesche HU et al. *Transplantation*. 2003;75:1291-1295.[1]

allograft nephropathy. In a population of kidney transplant recipients receiving cyclosporine, chronic allograft nephropathy was present in 92% of those who experienced an acute rejection episode in the first year compared with 57.9% of those who did not ($P<.001$).[19]

John's age at the time of transplantation, male gender, hypertension, and history of ischemic heart disease prior to transplantation are indicative of higher CV risk posttransplantation (Table 2).[5] His risk was increased further by the two acute rejection episodes, poorly controlled hypertension, dyslipidemia, and declining renal function.[1] Modifying his immunosuppression and more aggressive treatment of his hypertension and serum lipids were essential to reduce his CV risk and slow the progression of chronic allograft nephropathy. Sirolimus substitution for cyclosporine immunosuppression was a reasonable choice, based on clinical data.

Compared with cyclosporine, sirolimus is not nephrotoxic. In a study by Morales et al, at 2 years patients treated with sirolimus in combination with azathioprine and steroids or with MMF and steroids had a significantly higher glomerular filtration rate (GFR) than did patients treated with cyclosporine in the same combinations (69.3 mL/min and 56.8 mL/min, respectively; $P=.004$).[9] Patients treated with sirolimus also had a significantly lower incidence of treatment-emergent hypertension than did those in the cyclosporine group (30% and 48%, respectively; $P\leq.05$).[9]

However, sirolimus treatment is associated with dyslipidemia. In an analysis of two phase II studies comparing patients receiving sirolimus in combination therapy with those receiving cyclosporine in similar combination, those in the sirolimus group had significantly higher peak cholesterol and TG levels at 2 months.[20] Lipid parameters were controlled by reducing sirolimus trough levels and by using lipid-lowering drugs. After these adjustments at 2 months, lipid levels were statistically similar between the two groups from 12 months to 24 months.

Consistent with the observations of Morales et al, sirolimus-based therapy was associated with a lower incidence of treatment-emergent hypertension (29.6% with sirolimus and 47.5% with cyclosporine, $P<.024$). The calculated GFR was also significantly better at 2 years with sirolimus- than with cyclosporine-based therapy (51.3 mL/min and 65.1 mL/min, respectively; $P<.001$).[20]

Recent experimental evidence suggests that sirolimus may have antiatherogenic properties that ameliorate the effects of dyslipidemia.[21,22] These studies and more clinical data supporting the use of sirolimus in patients at high CV risk will be discussed in Case 4.

Table 2

Cardiovascular Risk Factors

Traditional	Nontraditional
Hypertension	Albuminuria
Diabetes	Homocysteinuria
Higher LDL cholesterol	Lipoprotein (a) and apolipoprotein (a) isoforms
Lower HDL cholesterol	Lipoprotein remnants
Smoking	Anemia
Physical inactivity	Abnormal calcium/phosphate metabolism
Menopause	Extracellular fluid overload
Family history of CVD	Electrolyte imbalance
Left ventricular hypertrophy	Oxidative stress
Older age	Inflammation (C-reactive protein)
Male gender	Malnutrition
	Thrombogenic factors
	Sleep disturbances
	Altered nitric oxide/endothelin balance

LDL, low-density lipoprotein; HDL, high-density lipoprotein; CVD, cardiovascular disease.

Adapted with permission from Sarnak MJ et al. *Circulation*. 2003; 108:2158.[5]

Case 2—Joy D. (Table 3)

Presentation

A 40-year-old African American woman, Joy D. is a homemaker and mother of three. Her endocrinologist has requested a consultation to consider modifications to her immunosuppressive regimen. Despite her efforts to lose weight and increase her activity, Joy has had difficulty achieving good glycemic control with neutral protamine Hagedorn insulin bid and regular insulin.

Joy received a primary kidney transplant 2 years ago. Her maintenance immunosuppressive regimen has been tacrolimus (4 mg bid adjusted to maintain trough levels of 5 to 8 ng/mL) and prednisone (7.5 mg/day). She has not experienced any episodes of acute rejection. However, 2 months posttransplantation she was diagnosed with new-onset diabetes mellitus.

Table 3

Case 2. Drug Sparing: Tacrolimus Dose Reduction

Name: Joy D. **Age:** 40 years **Race/Ethnicity:** African American

Baseline medications: tacrolimus (4 mg bid adjusted to maintain trough levels of 5-8 ng/mL), prednisone (7.5 mg/day)

Diagnosis: chronic allograft nephropathy and PTDM

Treatment: add MMF (1 g bid), decrease tacrolimus (2 mg bid adjusted to maintain trough levels of 2.5-4 ng/mL), prednisone (7.5 mg/day) unchanged

	Baseline	Presentation	Follow-up
Time after transplantation (mo)	6	24	30
Serum creatinine (mg/dL)	1.8	2.1	2.0
BUN (mg/dL)	20	28	25
Uric acid (mg/dL)	8	14	9
BP (mm Hg)	140/80	140/85	135/88
Fasting blood glucose (mg/dL)	106	120	103
HbA_{1c}(%)	5.1	9.3	7.6

PTDM, posttransplant diabetes mellitus; MMF, mycophenolate mofetil; BUN, blood urea nitrogen; BP, blood pressure; HbA_{1c}, hemoglobin A_{1c} (glycosylated hemoglobin).

Evaluation

Her serum creatinine level was 2.1 mg/dL at the consultation visit, up from the 6-month baseline value of 1.8 mg/dL. Her blood urea nitrogen (BUN) level (28 mg/dL) and uric acid level (14 mg/dL) were also elevated. Her most recent fasting glucose level was 120 mg/dL, and her most recent HbA_{1c} was 9.3%.

Diagnosis/Treatment Plan

Joy was diagnosed with chronic allograft nephropathy and PTDM. MMF (1g bid) was added to Joy's immunosuppressive treatment. Over the next 4 months, her tacrolimus dose was reduced by 50% to 2 mg bid with adjustments as needed to maintain trough levels of 2.5 to 4 ng/mL. She continued to take prednisone (7.5 mg/day).

Follow-up Report

When Joy returned to the clinic 6 months after the change in treatment (30 months posttransplantation), her serum creatinine was 2 mg/dL. Consistent with an improvement in renal function, her BUN and uric acid levels had also declined. Her fasting glucose level was 103 mg/dL and her HbA_{1c} had decreased to 7.6%. She reported that she needs 40% less insulin to keep her blood glucose levels stable.

Clinical Considerations

PTDM is common, affecting approximately 25% of kidney transplant recipients over the first 3 years posttransplantation.[4] Patients with PTDM have a higher risk of graft loss and death.[4] A number of factors have been identified that increase an individual's risk of developing PTDM. These include age at time of transplantation, obesity, ESRD due to glomerulonephritis, and African American ethnicity (Table 4).[4]

Because Joy is an African American, her risk of developing PTDM was between 1.6 and 3.3 times higher than if she were Caucasian.[4,23] In the general population, African Americans have a similar 1.6-fold greater risk of developing diabetes than Caucasians and have higher rates of hyperinsulinemia and insulin resistance.[15,24] Cosio et al have suggested that patients like Joy, who develop PTDM within 6 months posttransplantation, are likely to have had insulin resistance prior to transplantation that is exacerbated by immunosuppressive therapy with steroids and CNIs.[24]

Since 1995, the incidence of PTDM has increased almost 2-fold among kidney transplant recipients of all races.[24] A single-center study was conducted to assess the contributions of demographic and treatment changes to the upswing in PTDM. In the study population of 2078 patients who received transplants after 1983, those who received their transplants after 1995 were on average older and heavier. However, the marked increase in PTDM since 1995 was shown to be statistically independent of these factors, suggesting a role for newer immunosuppressive treatments.[24]

CNIs and steroids are associated with increased incidence of PTDM. The recent increase in the incidence of PTDM has occurred over a period of lower patient exposure to cumulative doses of steroids, as a result of fewer acute rejection episodes requiring steroid treatment.[24] To achieve the low rates of acute rejection, however, patients have been exposed to higher doses of CNIs. Although both are diabetogenic, tacrolimus is significantly more so than is cyclosporine.[23,25] The mechanisms for the effects of these drugs on glucose tolerance are not completely understood nor are the reasons for the greater diabetogenicity of tacrolimus. Experimental evidence suggests that tacrolimus inhibits insulin gene transcription leading to insulin-dependent PTDM.[26,27]

Despite the greater association with this serious complication, tacrolimus-based immunosuppression has been proven superior to cyclosporine-based treatments in reducing acute rejection rates.[23] Also, compared with cyclosporine-based immunosuppression over 5 years of follow-up, tacrolimus-based regimens were associated with significantly better graft survival and reduced requirements for antihypertensive and lipid-lowering agents.[28]

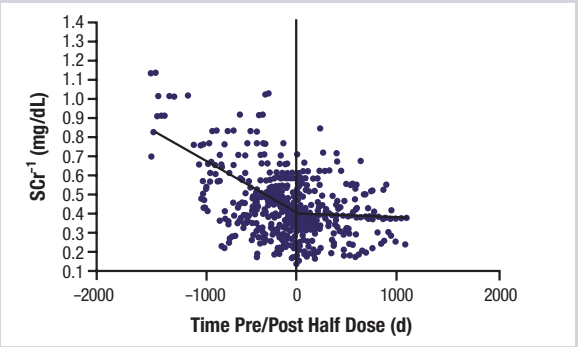
In an effort to optimize the use of tacrolimus in kidney transplant recipients, various combination regimens have been tested. The addition of MMF to tacrolimus has been shown to improve efficacy and safety. In a prospective, randomized trial of tacrolimus/prednisone versus tacrolimus/prednisone/MMF, the triple-therapy regimen resulted in a significant improvement in the incidence of rejection (44% vs 27%, respectively; P=.014).[6] The addition of MMF with no reduction in tacrolimus dose resulted in a nonsignificant decrease of approximately 50% in the incidence of PTDM (9.3% for double- and 4.7% for triple-drug treatment).[6]

Furthermore, these rates of PTDM for both treatment groups are substantially lower than those in other earlier reports. The authors suggested that, over time, tacrolimus treatment protocols have been refined, leading to an improved safety profile.[6]

In another study of CNI reduction in patients with chronic allograft nephropathy and hypertension, tacrolimus doses were gradually reduced by at least 50% over a period of 3 to 6 months.[29] The dose reduction was accomplished with the addition of MMF (average dose, 1.5 g/day). Steroid dosing was unchanged. The rate of decline in renal function was reduced over the 2-year follow-up in approximately 50% of patients in the reduced-dose group compared with those whose doses were not changed (Figure 2).[29] Significant reductions in nonfasting blood glucose levels (140.0 to 117.4 mg/dL, P<.05) and TC concentration (232.4 to 194.7 mg/dL, P<.05) were observed with CNI dose reduction.[29]

Figure 2

Change in Renal Function With Tacrolimus Dose Reduction in 33 Patients With Chronic Allograft Nephropathy Using Two-Phase Regression



SCr, serum creatinine.

Adapted with permission from Weir MR. *Transplant Proc*. 2001;33 (4 suppl):19S-28S.[30]

Tacrolimus is a potent immunosuppressive agent and an essential part of many immunosuppressive regimens. The inclusion of MMF in tacrolimus-based therapy can reduce adverse effects, including glucose intolerance, by allowing lower doses of tacrolimus.

CASE 3—ELEANOR J. (Table 5, page 6)

Presentation

Eleanor J. is a 60-year-old Caucasian woman retired from her job as a high school math teacher at the age of 55. She has been waiting for a kidney transplant for just over 1 year. She has been called to the transplant center because a deceased-donor kidney with zero mismatches has become available.

Evaluation

Eleanor has been diagnosed with ESRD due to autosomal dominant polycystic kidney disease. She has undergone hemodialysis 3 times per week for 14 months while on the kidney transplant waiting list. She has severe osteoporosis, which developed after she reached menopause, and she has a history of vertebral fractures. She is taking alendronate (10 mg qd). She also has been receiving calcitriol and calcium supplements.

Treatment Plan

Her initial immunosuppression included basiliximab induction along with sirolimus and tacrolimus (trough levels of 10 to 12 ng/mL). Pulse steroids were used during the first 5 days following surgery. Her alendronate (10 mg qd) was unchanged. She was to continue with calcitriol and calcium supplements as well.

Follow-up Report

At her 6-month follow-up visit, Eleanor had a serum creatinine of 1.8 mg/dL. This value is stable at the end of 1 year posttransplantation.

Clinical Considerations

Eleanor's history of severe osteoporosis requires careful consideration of which immunosuppressive regimen will least affect skeletal mass and calcium metabolism.

Renal osteodystrophy is a common complication of chronic kidney disease (CKD), resulting initially from loss of renal α-hydroxylase activity. Without adequate α-hydroxylase activity, vitamin D cannot be converted to its active metabolite. Compensatory increases in parathyroid hormone release and intestinal calcium absorption further perturb calcium and phosphate homeostasis and can eventually lead to irreversible parathyroid gland hyperplasia. Abnormalities in bone turnover occur early in CKD.[30] Declining levels of vitamin D can be measured in many patients with stage 2 CKD (creatinine clearance 60 to 90 mL/min/m^2), and levels reach the lower limit of normal (20 pg/mL) in stage 3 CKD (creatinine clearance 30 to 59 mL/min/m^2).

It is reasonable to assume that Eleanor's familial predisposition to postmenopausal osteoporosis was aggravated by a vitamin D deficiency related to her CKD and subsequent ESRD. She has responded well to treatment with alendronate, a bisphosphonate that acts to slow bone turnover.[31]

After transplantation, the vitamin D deficiency is expected to improve because of the restoration of kidney function. However, bone mineral density (BMD) decreases significantly in the first 6 months posttransplantation as a result of glucocorticoid therapy.[32,33] In a small study of 20 patients, lumbar bone density declined by 6.8% and 8.8% at 6 and

Table 4

Risk Factors for PTDM in a Population of 11,659 Medicare Beneficiaries Who Received Their First Kidney Transplant Between 1996 and 2000

Characteristic	Number With Characteristic (%)	Relative Risk for PTDM (95% CI)	*P*
Age (y)			
0-17	551 (4.7)	0.39 (0.28-0.56)	<.0001
18-44	5378 (46.1)	1.00 = reference	
45-59	3618 (31.0)	1.90 (1.73-2.09)	<.0001
≥60	2112 (18.1)	2.60 (2.32-2.92)	<.0001
Ethnicity			
African American	3646 (31.3)	1.68 (1.52-1.85)	<.0001
Caucasian	7336 (62.9)	1.00 = reference	
Hispanic	1437 (12.3)	1.35 (1.19-1.54)	<.0001
Non-Hispanic/unknown	10,222 (87.7)	1.00 = reference	
Male gender	6460 (55.4)	1.12 (1.03-1.21)	.0090
Body mass index (kg/m^2)			
≥30	2008 (17.2)	1.73 (1.57-1.90)	<.0001
<30	9651 (82.8)	1.00 = reference	
6 HLA mismatches	816 (7.0)	1.30 (1.07-1.58)	.0085
0 HLA mismatches	1275 (10.9)	1.00 = reference	
Hepatitis C positive	658 (5.6)	1.33 (1.15-1.55)	<.0001
Hepatitis C negative	11,001 (94.4)	1.00 = reference	
Glomerular nephritis as cause of ESRD	3659 (31.4)	0.80 (0.73-0.88)	<.0001
Other causes/unknown	10,544 (68.6)	1.00 = reference	
Immunosuppression			
Tacrolimus	2785 (23.9)	1.53 (1.29-1.81)	<.0001
No tacrolimus	8874 (76.1)	1.00 = reference	
Azathioprine	1739 (14.9)	0.84 (0.72-0.97)	.0160
No azathioprine	9920 (85.1)	1.00 = reference	
MMF	8228 (70.6)	0.78 (0.69-0.88)	<.0001
No MMF	3431 (29.4)	1.00 = reference	

PTDM, posttransplant diabetes mellitus; CI, confidence interval; HLA, human leukocyte antigen; ESRD, end-stage renal disease; MMF, mycophenolate mofetil.

Adapted with permission from Kasiske BL et al. *Am J Transplant*. 2003;3: 178-185.[4]

Table 5

Case 3. Drug Sparing: Tacrolimus Dose Reduction

Name: Eleanor J. **Age:** 60 years **Race/Ethnicity:** Caucasian

Baseline medications: sirolimus, tacrolimus (trough levels of 10-12 ng/mL), prednisolone (pulses), alendronate (10 mg qd), calcitriol (0.5 µg) and calcium supplements

Diagnosis: ESRD and severe osteoporosis

Treatment: steroid withdrawal after 5 days

	Baseline	Presentation	Follow-up
Time after transplantation (mo)	3	6	12
Serum creatinine (mg/dL)	1.9	1.8	1.8
BUN (mg/dL)	25	23	20
Uric acid (mg/dL)	8	8	8
BP (mm Hg)	138/80	139/82	135/82
Intact parathyroid hormone (pg/mL)	165	121	121

ESRD, end-stage renal disease; BUN, blood urea nitrogen; BP, blood pressure.

18 months, respectively.[32] This dose-dependent, prednisone-induced bone loss has been demonstrated in a number of other studies.[33-36]

The benefit of early steroid withdrawal on bone loss has been shown in a small study of 44 patients.[37] All patients were immunosuppressed initially with tacrolimus, MMF, and prednisolone. Over the course of the first 28 days post-transplantation, the prednisolone dose was decreased for all patients from 20 mg/day to 10 mg/day. At 3 months posttransplantation, they were randomized to continue receiving steroids or to be withdrawn from steroids over a period of 2 weeks.[37]

After 3 months of treatment (6 months posttransplantation), BMD and Z score of the lumbar spine decreased significantly from the 3-month baseline in patients who continued steroid treatment (–1.4 ± 3.2% and –0.3 ± 0.3%, respectively; $P<.05$ for both comparisons). The lumbar spine T score tended to decrease in this treatment group also. Those patients who were withdrawn from steroids had no significant change in BMD, Z score, or T score of the lumbar spine. These values were significantly different from those in the steroid-continued group. The BMD, Z score, and T score of the femoral neck decreased in the steroid-continued group with no change in those patients withdrawn from steroids. However, the differences were not significant.[37] Although the bone loss was not reversed in this study, none of the patients were receiving bisphosphonate treatment or supplementation with calcium or vitamin D. These results suggest that a strategy reducing steroid exposure can limit bone loss posttransplantation for a patient such as Eleanor. It is clear that steroids can cause osteoporosis, but whether steroid-sparing improves osteoporosis remains to be proven.

An even greater concern regarding steroid use in kidney transplant recipients is the impact of treatment on CV risk. Rogers et al used a modified Framingham risk calculation of coronary heart disease (CHD) risk over the course of the first year posttransplantation in 183 kidney transplant recipients. These patients were all enrolled in early steroid-withdrawal trials. This unpublished data suggests that early steroid withdrawal may benefit patients by reducing CV risk.[38]

Successful withdrawal of steroids at 5 to 6 days post-transplantation has been reported in a study of 14 primary kidney transplant recipients.[39] The immunosuppressive regimen included basiliximab induction, sirolimus (target levels of 8 to 15 ng/mL, 0 to 5 months, and 6 to 12 ng/mL, 6 to 12 months), and tacrolimus (0.05 mg/kg with target levels of 6 to 9 ng/mL). Acute rejection did not occur after steroid withdrawal (posttransplant day 5) in the first 6 months posttransplantation.[39]

Sirolimus alone is not nephrotoxic, as has been discussed. However, in combination with CNIs, sirolimus is associated with a dose-dependent increase in nephrotoxicity.[9,40] Although no data regarding nephrotoxicity were reported by Vincenti et al,[39] the very low dose used in their protocol is not likely to be problematic. In another small study, patients who received antithymocyte globulin antibody induction and steroids were randomized to receive a low dose of tacrolimus (trough levels of 5 to 10 ng/mL) and standard-dose sirolimus (trough levels of 10 to 15 ng/mL) (group A) or standard doses of tacrolimus (trough levels of 10 to 15 ng/mL) and low-dose sirolimus (trough levels of 5 to 10 ng/mL) (group B). At 6 months posttransplantation, the acute rejection rates were 6% and 5% for groups A and B, respectively. However, 7 of the 16 patients (38%) in group B had to be discontinued because of tacrolimus nephrotoxicity. None of the patients in group A were discontinued.[40] These findings suggest that tacrolimus combined with sirolimus may reduce the risk of acute rejection for certain renal transplant recipients. However, the authors advised that the dose of these immunosuppressants should be carefully considered in order to avoid adverse events.

Recently, a study of 150 kidney transplant recipients that compared the efficacy of various doses (and blood levels) of tacrolimus combined with sirolimus or MMF was published. The results of that study are consistent with the observation that lower exposure to a CNI can result in a decrease in nephrotoxicity as long as the net state of immunosuppression is ensured by other agents.[41,42] Tacrolimus was instituted at a dose of 0.1 mg bid with an initial target trough level of 10 ng/mL for all patients. For those receiving sirolimus (target trough levels of 8 ng/mL), the tacrolimus dose was decreased and blood trough levels decreased first to 6 to 8 ng/mL at 6 months and then to 6 ng/mL at 1 year. Those receiving MMF (1 g bid) continued the tacrolimus target trough level of 10 ng/mL until 1 year posttransplantation at which time the target trough level was reduced to 8 ng/mL. There were no significant differences in the overall incidence of acute rejection between the various study areas. These results suggest that sirolimus can be used safely with low doses of tacrolimus. Over 12 months of follow-up, there were no acute rejection episodes in either group. Patient survival, graft survival, and serum creatinine values were similar between the two treatment groups.[41]

In summary, the elimination of steroids is important in patients with existing osteoporosis. It is important, however, that optimal immunosuppression is provided to the renal transplant recipient. The use of monoclonal antibody induction and an immunosuppressive protocol containing sirolimus and low-dose tacrolimus (but no steroids) is a safe and effective approach to achieve this goal.

Case 4—George G. (Table 6)

Presentation

George G. is a 52-year-old Caucasian man who owns a restaurant. He has had to turn over most of his business responsibilities to his daughter because of a heart attack and worsening CV disease.

George has been diagnosed with chronic allograft nephropathy and needs retransplantation 6 years after receiving his first kidney transplant from a deceased donor. Two episodes of acute rejection occurred in the months following this primary transplantation: the first at 4 weeks that resolved with steroid therapy and a second at 3 months that was successfully treated with antithymocyte globulin.

His 6-month serum creatinine level was 1.6 mg/dL, but had gradually increased to 2.1 mg/dL by 1 year posttransplantation. He was dipstick positive for proteinuria and his urinalysis showed a 2+ protein. His BUN was 35 mg/dL. He was diagnosed with chronic allograft nephropathy at that time (1 year post–primary transplantation), and his renal function has continued to decline. He has been on dialysis for the past 3 months.

George has a history of hypertension and had a myocardial infarction 3 years ago. During the first 3 years posttransplantation, his physician had difficulty controlling his BP. Since his heart attack, George has modified his diet and tries to take short walks regularly. His hypertension has been well controlled with metoprolol (50 mg bid) and amlodipine (20 mg qd). During his physical exam following transplantation, his blood pressure was 126/76 mm Hg.

Treatment Plan

The initial immunosuppression regimen to be used following the second transplantation included daclizumab induction, sirolimus (2 mg/day), cyclosporine, and steroids for 3 months. The patient continued to receive metoprolol. Based on the lipid profile, atorvastatin 10 mg/day could be added. Cyclosporine was to be withdrawn over a 2-month period if George was acute-rejection free at the end of the first 3 months posttransplantation.

Clinical Considerations

The loss of George's primary kidney transplant was undoubtedly the result of a combination of factors that led to chronic allograft nephropathy and progressive loss of renal function. As was discussed for John R., the acute rejection episodes, hypertension, and ischemic heart disease placed George at high risk of both CV events and graft loss. The cyclosporine-sparing protocol with daclizumab induction, sirolimus, and steroids was chosen to provide George with a high level of immunosuppression in the first months post-transplantation. The gradual withdrawal of cyclosporine was done with the expectation that a lower cumulative dose would protect the transplanted kidney from long-term cyclosporine nephrotoxicity.

Sirolimus-based therapy after cyclosporine withdrawal has been shown to be highly effective and associated with significantly better renal function than cyclosporine monotherapy over 3 years.[43] Four hundred thirty patients who received sirolimus, cyclosporine, and steroids for 3 months post–kidney transplantation were randomly assigned to continue the three-drug treatment or to undergo cyclosporine withdrawal and remain on sirolimus and steroids. After 3 years of follow-up, graft survival and patient survival were statistically similar in the two groups.[43]

However, renal function was significantly better in the cyclosporine-withdrawal group. Serum creatinine levels were 1.9 mg/dL in the cyclosporine-continued group and 1.6 mg/dL in the cyclosporine-withdrawal group ($P<.001$) by intent-to-treat analysis. Calculated GFR was also significantly better at all time points after cyclosporine withdrawal for those patients who completed study treatment (Figure 3, page 8).[44] Moreover, the rate of change in GFR was 0.827 ± 0.449 ml/min per year in the cyclosporine-withdrawal group compared with –3.037 ± 0.453 mL/min per year ($P<.001$ for the difference). These results indicate that, when the sirolimus-cyclosporine-steroid group was compared with the sirolimus-steroid group, both had similar rates of acute rejection; however, the latter group experienced significantly better renal function.[43]

As has been discussed, decreased renal function is a major risk factor for CV death in the transplant population. Other CV parameters were better or the same in the cyclosporine-withdrawal group. Cyclosporine withdrawal led to statistically significant and sustained improvement in systolic and diastolic BP (Figure 4, page 8).[43] Mean serum TC levels peaked at month 2 and decreased through month 9 and remained stable for both treatment groups. At 36 months, no significant differences in LDL-C, HDL-C, or TG values were reported between the treatment groups, although TC values tended to be higher for the cyclosporine-withdrawal group. Statins were given to 75% and 78% of individuals in the cyclosporine-continued and cyclosporine-withdrawal groups, respectively. Mean hemoglobin levels were significantly higher in the cyclosporine-withdrawal group as well at 36 months posttransplantation.[43]

In light of early reports that sirolimus increased cyclosporine toxicity, using this combination to preserve renal function

Table 6

Case 4. Drug Elimination: Cyclosporine Withdrawal

Name: George G. **Age:** 52 years **Race/Ethnicity:** Caucasian

Baseline medications: sirolimus (2 mg/day), cyclosporine, steroids, metoprolol (50 mg bid), amlodipine (20 mg qd)

Diagnosis: chronic allograft nephropathy and ESRD requiring retransplantation

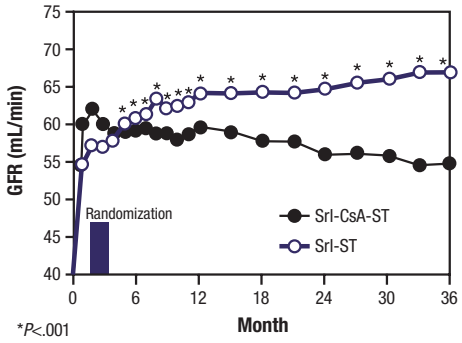
Treatment: sirolimus (2 mg/day), cyclosporine, steroids, metoprolol (50 mg bid), amlodipine (20 mg qd); at 3 months posttransplantation, cyclosporine withdrawn over a 2-month period; atorvastatin (10 mg/day)

	Baseline	Presentation	Follow-up After Retransplantation
Time after transplantation (mo)	6	12	3
Serum creatinine (mg/dL)	1.6	2.1	1.0
BUN (mg/dL)	NR	35	19
Uric acid (mg/dL)	NR	5	6
Urinalysis	NR	2+ protein	NR
BP (mm Hg)	135/88	135/85	126/76

ESRD, end-stage renal disease; BUN, blood urea nitrogen; NR, not reported.

Figure 3

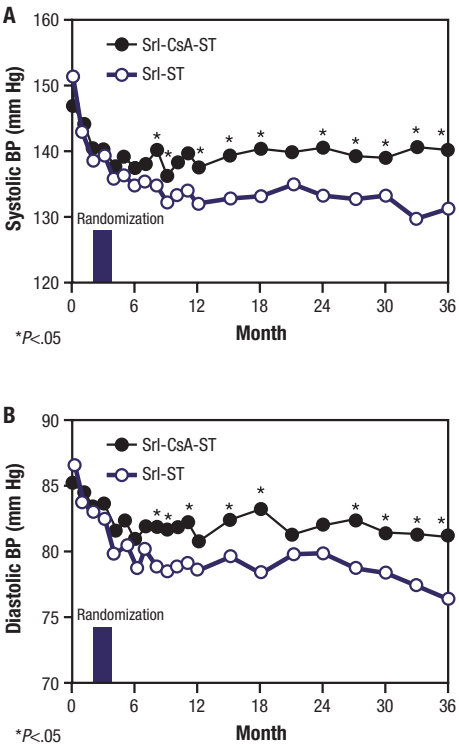
Calculated Glomerular Filtration Rate (GFR) in Patients Who Completed 36 Months of Therapy With Sirolimus (SrI) and Steroids (ST) Plus Continuous Cyclosporine (CsA) or After CsA Withdrawal



Adapted with permission from Kreis H et al. *J Am Soc Nephrol*. 2004;15:809-817.[43]

Figure 4

Mean Systolic (A) and Diastolic (B) Blood Pressure (BP) in Patients Who Completed 36 Months of Therapy With Sirolimus (SrI) and Steroids (ST) Plus Continuous Cyclosporine (CsA) or After CsA Withdrawal



Adapted with permission from Kreis H et al. *J Am Soc Nephrol*. 2004;15:809-817.[43]

may at first appear counterintuitive. It is important to emphasize that in addition to the robust results from the cyclosporine-withdrawal study just discussed, the safety of sirolimus combined with standard-dose cyclosporine has been demonstrated in a worldwide, randomized, phase III study.[44] A total of 576 recipients of primary mismatched renal allografts were randomized to receive standard therapy with cyclosporine and steroids plus placebo, sirolimus 2 mg/day, or sirolimus 5 mg/day. At 3 months and 6 months posttransplantation, there were no significant differences in serum creatinine in the three treatment groups. However, sirolimus 5 mg/day led to a significant decrease in GFR at 3 months compared with sirolimus 2 mg/day and placebo. A similar difference between sirolimus 5 mg/day and placebo was seen at 6 months. At 6 months, compared with placebo, the incidence of biopsy-proven acute rejection was decreased by 40.5% (P=.003) with sirolimus 2 mg/day and by 53.7% (P<.001) with sirolimus 5 mg/day.[44] These results confirm that sirolimus 2 mg/day combined with standard cyclosporine and steroid dosing is safe and significantly reduces the rate of acute rejection following kidney transplantation.

Another important consideration in using sirolimus in patients with serious CV complications is the possible antiatherosclerotic effect of this drug. As has been discussed elsewhere in this monograph, sirolimus is associated with dyslipidemia, most notably elevated cholesterol and TG levels. Although these lipid profiles are associated with increased risk of CV events, recent studies suggest that sirolimus may have a beneficial effect on the chronic inflammatory process underlying atherosclerosis. Such a change may actually improve CV risk despite increases in circulating lipids.[21,22]

TOR inhibitors, including sirolimus and another experimental agent, everolimus, impede the proliferation of an array of cell types, including T cells and vascular smooth muscle cells, which are involved in vascular injury and inflammation.[45] This antiproliferative activity is thought to contribute to the arrested progression of intimal thickening observed in animal models of vascular injury.[46,47]

Clinical evidence consistent with this hypothesis is based on patients with acute coronary events. Sirolimus-coated stents have been shown to minimize neointimal proliferation.[48] Furthermore, in heart transplant recipients treated with everolimus, similar benefit was shown in limiting intimal thickening compared with azathioprine treatment at 12 months posttransplantation.[49]

SUMMARY

As illustrated in the four cases presented here, new immunosuppressive regimens promise to improve the long-term health of kidney transplant recipients. The greater number of available immunosuppressive agents, coupled with more experience using these agents in the clinical setting, has created opportunities to customize immunosuppressive therapies based on specific patient needs.

The next monograph in this educational series will explore in greater detail the benefits and options of customized immunosuppressive protocols with the target of preserving long-term renal function.

A Case Study Approach to the Clinician's Challenge in Preserving Long-term Renal Function

CE Posttest and Evaluation

Release Date: November 2004 Expiration Date: November 30, 2005

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Posttest

1. Data from a follow-up in kidney transplant recipients treated initially with cyclosporine or azathioprine indicate that the graft survival benefit with cyclosporine is no longer significant after ___ year(s) of treatment.
   a. 1
   b. 3
   c. 5
   d. 10

2. Cyclosporine and tacrolimus treatments have been associated with:
   a. Progressive decrease in renal function
   b. Hypertension and dyslipidemia
   c. Posttransplant diabetes mellitus
   d. All of the above
   e. None of the above

3. The 6-year graft survival rate for individuals who did not recover baseline renal function after acute rejection was:
   a. 16.8%
   b. 50.4%
   c. 72.7%
   d. Almost 92%
   e. None of the above

4. In a study of 1295 individuals who had functioning grafts 1 year after transplantation less than 4% of these patients were normotensive and more than 50% had stage 1 or 2 hypertension.
   a. True
   b. False

5. Compared with cyclosporine, sirolimus treatment:
   a. Is not nephrotoxic
   b. Has a significantly lower incidence of treatment-emergent hypertension
   c. Is associated with dyslipidemia
   d. All of the above
   e. None of the above

6. The inclusion of mycophenolate mofetil in tacrolimus-based therapy can reduce glucose intolerance by lowering the dose of tacrolimus required to prevent rejection.
   a. True
   b. False

7. In combination with tacrolimus, sirolimus is associated with a dose-dependent increase in nephrotoxicity.
   a. True
   b. False

8. Sirolimus is associated with dyslipidemia and adversely affects the chronic inflammatory process underlying atherosclerosis.
   a. True
   b. False

9. Cyclosporine withdrawal has led to statistically significant and sustained improvement in systolic and diastolic blood pressure.
   a. True
   b. False

10. Hypertension generally occurs at younger ages in African Americans than in Caucasians and results in higher rates of stroke, cardiovascular disease, and cardiovascular death.
    a. True
    b. False

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Posttest Answer Key

1. a b c d	3. a b c d e	5. a b c d e	7. a b	9. a b
2. a b c d e	4. a b	6. a b	8. a b	10. a b

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The University of Minnesota would appreciate your comments regarding the quality of the information presented.

1. The program objectives were fully met.
   ❑ Strongly Agree ❑ Agree ❑ Disagree ❑ Strongly Disagree

2. The quality of the educational process (method of presentation and information provided) was satisfactory and appropriate.
   ❑ Strongly Agree ❑ Agree ❑ Disagree ❑ Strongly Disagree

3. The educational activity has enhanced my professional effectiveness and improved my ability to treat/manage patients.
   ❑ Strongly Agree ❑ Agree ❑ Disagree ❑ Strongly Disagree ❑ N/A

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   ❑ Strongly Agree ❑ Agree ❑ Disagree ❑ Strongly Disagree ❑ N/A

5. The information presented was free of promotional or commercial bias.
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   _____

   _____

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