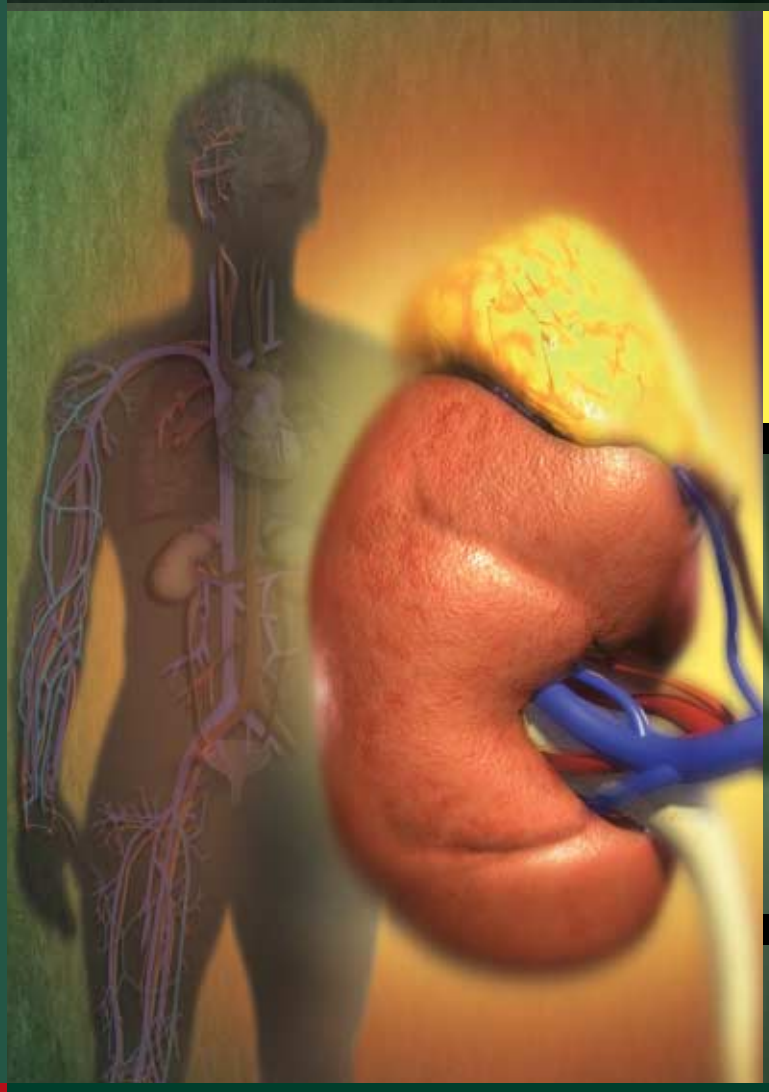
Implications of PRESERVING LONG-TERM RENAL FUNCTION After Renal Transplantation

PRESENTED BY:

NATIONAL INSTITUTE OF ALLERGY AND INFECTIOUS DISEASES OF
THE NATIONAL INSTITUTES OF HEALTH
U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES

Modifiable and Nonmodifiable Donor and Recipient Factors as Targets for Preservation of Renal Function



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Introduction

Acute rejection rates following renal transplantation have declined dramatically with the use of calcineurin inhibitors, cyclosporine, and tacrolimus. However, overall graft survival has not improved to the same degree.[1]

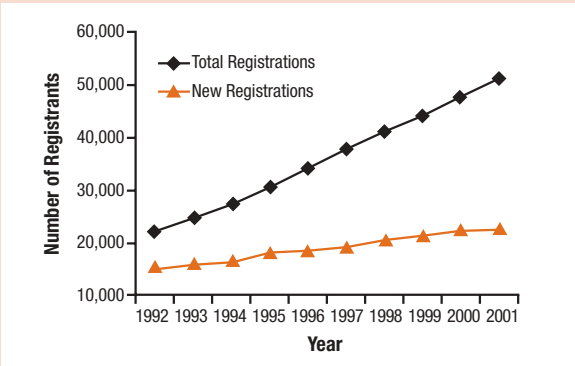
The successful prevention of acute rejection episodes in recent years has focused attention on chronic allograft nephropathy (CAN), which is now the leading cause of late renal transplant failure. There is a growing body of evidence to support the hypothesis that CAN and graft loss result from a proinflammatory state that leads to progressive allograft injury and, possibly, host systemic vascular injury. Many of the risk factors for graft loss can promote inflammation and renal injury.

Beyond the considerable morbidity and even mortality associated with graft failure, the need for retransplantation adds to the already-overextended demand for donor kidneys. Between 1992 and 2001, the number of individuals on the waiting list for kidney transplantation increased by 132% despite the doubling of live-donor kidney transplants (up 135%) and the increased use of so-called expanded donor criteria over the same time period.[2] The greater demand for donor kidneys has resulted in an alarming increase in waiting times for transplantation. In 2001, 40% of candidates for kidney transplantation had been waiting for at least 2 years, and the waiting time in many parts of the United States now exceeds 5 years (Figure 1).[2] Although the rate of increase in waiting time for transplantation has slowed, the incidence of end-stage renal disease (ESRD) continues to rise, and the eligibility criteria for kidney transplant recipients have been expanded.[2] Accordingly, the available evidence suggests that waiting times will continue to increase, and approaches designed to improve long-term graft survival and reduce the need for retransplantation are essential.

This fourth monograph in this educational series will focus on modifiable and nonmodifiable risk factors for graft loss. Evidence suggesting that immunologic and nonimmunologic renal injuries are common to many of these risk factors will be presented, and possible therapeutic approaches will be explored.

Figure 1

Growth in the Waiting List for Deceased-Donor Kidneys by Total Registrations at Year End and New Registrations per Calendar Year, 1992-2001



Source: *2003 OPTN/SRTR* Annual Report, Tables 5.1, 5.2.[32]

Risk Factors for Graft Loss

Cecka et al were among the first to recognize that analysis of donor and recipient risk factors could provide meaningful predictive information regarding the probability of 1-year graft and patient survival.[3] Their 1992 analysis of outcomes of almost 20,000 deceased donor kidney transplant recipients included in the United Network for Organ Sharing Scientific Renal Transplant Registry revealed that graft loss within the first year posttransplantation was associated with delayed graft function (DGF; defined as anuria during the first 24 hours posttransplantation and/or dialysis during the first week), acute rejection episode(s) during the initial hospitalization, and serum creatinine levels >2.5 mg/dL at discharge. Notably, multiple episodes of acute rejection were associated with the lowest incidence of graft survival (Table 1).[3] The three most influential donor-related risk factors for DGF included prolonged cold ischemia time, death due to stroke, and donor age >50 years.[3] This initial report provided the basis for many subsequent analyses documenting the donor and recipient-related risk factors that have consistently represented negative prognostic indicators of graft survival, possibly even beyond the first year; these include DGF, acute rejection, and elevated serum creatinine values >2.0 mg/dL at 6 months posttransplantation, along with African-American race of the transplant recipient and the age of the donor (Table 2).[4-6]

Modifiable Donor-Related Risk Factors

Among donor-related risk factors shown to influence outcomes, only DGF associated with prolonged cold ischemia time and possibly ischemia-reperfusion injury have some potential for modification. Although initiated by nonimmunologic events, effects of ischemia and reperfusion are similar to those observed with alloimmune reactions, that is, they may result from inflammatory responses to

Table 1

Effect of the Number of Acute Rejection Episodes During Initial Hospitalization on 1-Year Deceased-Donor Renal Allograft Survival[3]

	1-Year Graft Survival (%)
Rejection free	85.1
1 rejection episode	67.2
Multiple rejection episodes	56.6

Table 2

Risk Factors for Chronic Allograft Rejection

Variable	Risk Ratio (*P*)
Acute rejection	2.3 (.0001)
Serum creatinine >2.0 mg/dL at 6 months	2.6 (.0001)
African-American ethnicity (recipient)	2.1 (.0006)
Donor age ≥50 years	1.8 (.006)

Adapted with permission from Flechner SM et al. *Transplantation*. 1996;62: 1235-1241.[4]

injury.[7] DGF is thought to cause acute endothelial damage, triggering a self-perpetuating, inflammatory cycle including increased expression of cellular adhesion molecules, chemokines, and cytokines. Release of oxygen-free radicals by immune cells also appears to perpetuate the proinflammatory state, possibly exacerbating host alloimmunity.[7]

Experimental evidence suggests that overexpression of genes encoding proteins that reduce oxidative stress may protect against injury secondary to ischemia and reperfusion. This suggests that regulation of cellular signals may provide a target for reducing the consequences of ischemia and perfusion.[8]

Other research suggests that strategies to block cytokine responses may provide another therapeutic approach. Inflammatory cytokines, produced by T-helper type 1 cells such as tumor necrosis factor and interferon (IFN)-γ, have been implicated in the pathobiology of graft vascular injury associated with chronic allograft nephropathy, and approaches such as targeted antibody therapy have been suggested in that regard.[9-11] Additionally, results demonstrating prolonged allograft survival in cynomolgus monkeys using an inhibitor of Janus kinase 3, an enzyme critical for signaling by multiple cytokines, also suggests that cytokine blockade may provide an attractive target.[12] Together, findings such as these suggest that interruption of inflammatation may provide a therapeutic target to reduce risk of renal damage initiated by specific alloimmune or nonimmune events.

Modifiable Recipient-Related Factors

The profile of "typical" kidney transplant candidates has changed during recent years, and the potential for modifying recipient-related risk factors is limited. However, opportunities for more effective management should similarly be applicable in our efforts to improve long-term outcomes.

Waiting time on dialysis consistently represents the strongest independent, potentially modifiable risk factor for graft loss.[13] The 5-year and 10-year graft survival rates were 58% and 29%, respectively, for patients who were on dialysis for longer than 2 years compared with 78% and 68%, respectively, for those who were on dialysis for less than 6 months (P<.001 for both comparisons).[13]

Prolonged dialysis has also increased the administrative burden, particularly as the population on dialysis has become more complicated with multiple comorbidities potentially impacting the suitability for transplantation. Longer waiting times in conjunction with broadening eligibility criteria for transplantation, including medical comorbidities and more advanced age, present new challenges to the transplant community. Between 1992 and 2001, the mean age of patients on the waiting list for a kidney transplant increased from 42.6 years to 48.8 years, and the percentage of individuals on the waiting list older than age 65 years increased by more than 7%.[2] Increased recipient age, with its more serious comorbidities, may also influence long-term outcomes. Although strategies designed to directly assess the impact of aggressive management of these comorbidities (eg, hypertension, diabetes, or dyslipidemia) pre- or posttransplantation on long-term graft survival have not yet been detailed, this too seems to represent a logical area deserving attention. A disproportional incidence of hypertension and diabetes among African-Americans, compared to other racial groups, results in a high rate of ESRD and need for renal transplantation.[2]

Seeking to remedy this problem, Roberts et al suggested modifications to the organ allocation algorithm that will de-emphasize HLA-B matching.[14] Their rationale was that the overall clinical benefit associated with HLA-B matching is small and may be overridden by issues such as prolonged cold ischemia time. Using this strategy, Roberts et al estimated that the number of transplant procedures among nonwhite (ie, African-Americans, Asians, Hispanics, other ethnic groups) would increase by 6.3%, with only an associated 2% increase in the rate of graft loss.[14] Therefore, approaches that de-emphasize matching HLA-B seem unlikely to greatly reduce overall success rates, will reduce the incidence of DGF due to prolonged cold ischemia time, and at the same time, it may reduce the relative disadvantage to African-Americans.

The presence of preformed anti-HLA antibodies, measured as panel reactive antibodies (PRA) represent another influence on long-term graft survival. Although the overall rate of anti-HLA presensitization has fallen, it has been suggested that women and African-Americans are more likely to be sensitized (PRA >20%) than are men and members of other racial and ethnic groups awaiting kidney transplantation.[2] The use of erythropoietin to treat anemia has reduced the need for transfusions[15] and may account for the lower rate of anti-HLA presensitization. Regardless, the problem of HLA sensitization continues to represent an important barrier to transplantation for many, and it may select a group at increased risk for long-term graft failure.

Renal Function and Graft Loss

Although it has been apparent for many years that measures of renal function correlate strongly with graft half-life and it has been suggested that injury leading to diminished renal function may reflect the primary result of many risk factors for graft loss, research evaluating possible intervention strategies in this regard has been limited. Again, it was observed many years ago that early renal dysfunction, whether it was the result of acute rejection (immunologic) or nonimmunologic events, represents a negative predictor of 1-year graft survival.[3] This finding has been repeatedly confirmed, and a recent example reported by Flechner et al found that a serum creatinine ≥2.0 mg/dL by 6 months more than doubled the risk of chronic allograft nephropathy (P=.0001) (Figure 2).[4] For kidney transplantations performed between 1988 and 1998, the relative hazard for graft failure was 1.63 (95% confidence interval [CI], 1.61-1.65; P<.0001) for each incremental increase of 1.0 mg/dL of serum creatinine at 1 year.[16]

An important observation in this regard has been that when the serum creatinine returns to its baseline value after treatment of acute rejection, the risk of later CAN is dramatically diminished. An example of such was reported by Meier-Kriesche et al, who found that the serum creatinine value at 6-months after transplantation represents a better correlate of long-term graft survival (3-year and 6-year) versus acute rejection alone (Figure 3).[1] Again, the authors

found that when the serum creatinine returned to the 6-month value following an acute rejection episode, the 3- and 6-year graft survival rates were similar to those in individuals who never experienced acute rejection. This observation contrasted sharply with the situation seen in those whose serum creatinine remained elevated (19% and 23% lower graft survival at 3 and 6 years, respectively) versus those who never experienced acute rejection ($P<.0001$).[1]

Although current immunosuppressive protocols contributed to a reduction in acute rejection rates by nearly half over the first 2 years posttransplantation, the expected increase in long-term graft survival has not been observed.[1]

Although long-term data are limited, a study by Marcén et al compared the outcome of deceased-donor renal transplant recipients treated with cyclosporine to that of a similar number of recipients treated with azathioprine over a 10 year period. The benefit of cyclosporine treatment was statistically significant in the first 3 years posttransplantation. After the 3-year mark, however, the differences in the treatment groups was not statistically significant, although graft survival rate in the cyclosporine group declined at a lower rate.[17]

Chronic allograft nephropathy was the cause of graft loss in 40.6% of cyclosporine-treated patients compared with 16.8% of those in the azathioprine-treatment group ($P=.008$).[17] By 10 years, the graft survival rates were similar regardless of initial treatment.[17] Taken in sum, these findings suggest that successful treatment of acute rejection has unmasked the importance of renal function in long-term graft survival, raising questions about the impact of drug-induced nephrotoxicity that accompanies the use of medications such as calcineurin inhibitors.

The role of calcineurin inhibitors in renal dysfunction posttransplantation is suggested by the development of renal dysfunction in transplant recipients of extrarenal organs. The 5-year cumulative incidence of chronic renal failure ranges from a low of 6.9% in heart-lung transplant recipients to a high of 21.3% for intestinal transplant recipients.[18] The health of the recipients' kidneys at the time of transplantation was a major factor in whether chronic renal failure developed posttransplantation.[18] In addition, Goldstein et al showed that among cardiac transplant recipients, the proportion of patients with elevated serum creatinine levels correlated with exposure to cyclosporine for at least 3 years (Figure 4, page 4).[19] By 3 years posttransplantation, mean serum creatinine levels in these patients rose by 125% ($P<.001$ vs pretransplant values).[19]

Vascular Rejection and Graft Loss

Renal transplant biopsies reveal that acute cellular rejection is associated with inflammatory cell infiltration into the cortical interstitium and tubules (tubulitis) or the subendothelium of the arteries (intimal arteritis).[20] Occasionally, infiltrates are found in both compartments (transmural arteritis).[20] Acute rejection with intimal arteritis is designated by the Banff '97 classification as type 2A or 2B, depending on the extent of arteritis.[21]

Distinguishing between these histologic differences is potentially important because they have been associated with different clinical responses to antirejection treatments and, ultimately, with graft survival.[20,22,23] Additionally, the

Figure 2

Kaplan-Meier Estimates of Time to Chronic Rejection (Percentage of Patients Who Remain Free of Chronic Rejection) Plotted According to 6-Month Serum Creatinine <2 mg/dL or ≥2 mg/dL

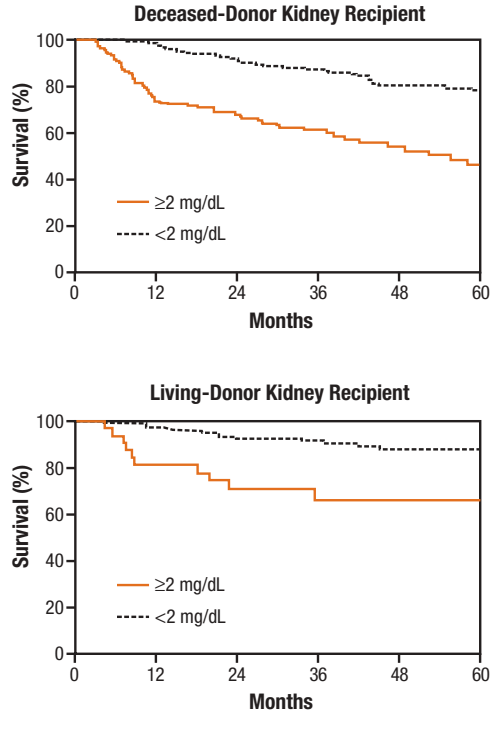


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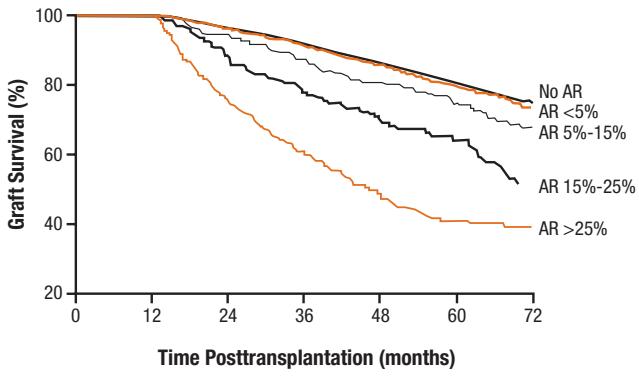
Figure 3

Kaplan-Meier Plot of Overall Graft Survival by Acute Rejection (AR)/Glomerular Filtration Rate Grouping Levels



Reprinted with permission from Meier-Kriesche HU et al. *Am J Transplant*. 2004;4:378-383.[1]

effects of early vascular rejection posttransplantation may exhibit delayed pathology, manifesting several years later. For example, a single-center study of 428 kidney transplant recipients reported that individuals who experienced acute vascular rejection in the first 3 months posttransplantation had a 1-year graft survival rate of 50% and a 5-year rate of 34% versus 87% and 71%, respectively, for patients experiencing pure interstitial rejection and 88% and 74%, respectively, for patients with no early acute rejection.[24] Similar results have been reported using tacrolimus-based immunosuppression after kidney transplantation with 67% 5-year graft survival among recipients experiencing acute vascular rejection, compared to 93.8% among a comparison group experiencing interstitial rejection without vascular involvement and 90.2% among those with no rejection (log-rank *P*=.01, vascular rejection vs other groups).[25]

Other clinical results have provided support for the suggestion that allograft vascular injury may be causally related to chronic rejection and graft loss. Sijpkens et al compared outcomes for patients with chronic allograft nephropathy with and without histologically documented vasculopathy.[26] Serum creatinine levels and creatinine clearance were significantly worse at 6 months in those with vasculopathy than in those without (or for creatinine clearance, 0.58 [0.44-0.75] per 10-mL/min increase). This observation is consistent with the predictive value of 6-month renal function for long-term graft survival described elsewhere and supports a correlation between vasculopathy and early renal dysfunction.[26]

Experimental support of the hypothesis that intimal arteritis is a precursor of the lesion of chronic rejection has also been reported. In severe combined immunodeficient (SCID) mice receiving human peripheral blood mononuclear cells prior to transplantation of size-matched human muscular arteries into the infra-abdominal aorta, lesions that were indistinguishable from those seen in human arteries during acute vascular rejection were identified (Figure 5).[27]

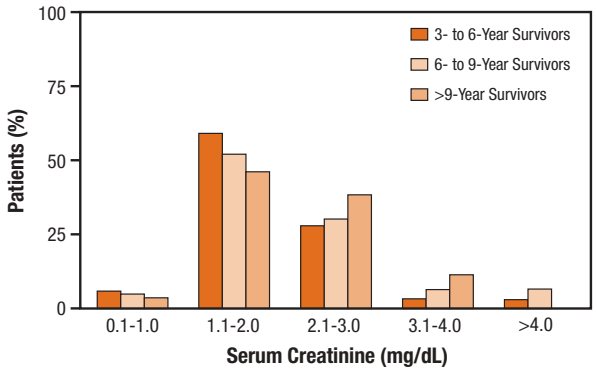
Evidence has suggested a possible etiologic relationship between this allograft arterial injury and inflammatory cytokines such as IFN-γ.[28] Additionally, agents such as sirolimus and neutralizing antibodies directed toward IFN-γ have been demonstrated to ameliorate the arterial lesion in a skin graft model evaluating the microvasculature, as well as using the above arterial allograft model.[10] Sirolimus administration has also been demonstrated to abrogate allograft arterial injury using the nonhuman primate model (cynomolgus monkeys) (Figure 6).[29]

Beyond the preclinical results, clinical evidence has also suggested a beneficial effect of sirolimus on intimal injury of nonimmunologic as well as of alloimmune etiology. The initial evidence came from a preliminary evaluation of sirolimus-impregnated coronary stents placed in patients experiencing acute coronary artery occlusion. Following percutaneous angioplasty placement of these sirolimus-impregnated stents was associated with a reduction in the incidence of intimal hyperplasia and resulting restenosis (Figure 7).[30] Additionally, cardiac transplant recipients treated with another TOR inhibitor, everolimus, demonstrated reduced intimal disease when compared to similar patients receiving azathioprine treatment at 12 months posttransplantation, although serum creatinine levels were significantly higher in the everolimus group than the azathioprine group.[31]

A growing body of evidence continues to provide support to the association between allograft vascular injury and later development of chronic vascular disease. Additionally, experimental support is more substantial, but a growing clinical experience suggests that modification of immunosuppressive therapy using strategies to reduce the reliance on the calcineurin inhibitors, favoring the newer class of TOR inhibitors, sirolimus and everolimus, may ameliorate chronic allograft vascular disease.

Figure 4

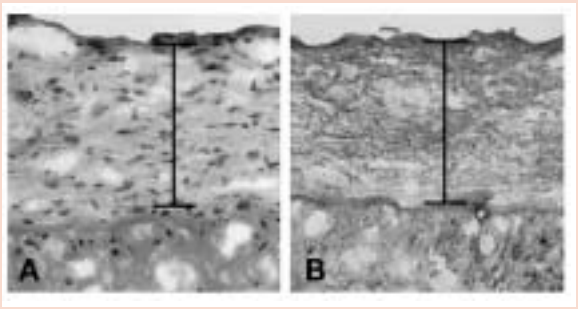
Distribution of Serum Creatinine Among 293 Adult Cardiac Allograft Recipients Exposed to at Least 3 Years of Cyclosporine. Patients Have Been Arbitrarily Categorized Into 3 Groups, According to Survival After Transplantation (ie, Length of Exposure to Cyclosporine)



Adapted with permission from Goldstein DJ et al. *Transplantation*. 1997;63:664-668.[19]

Figure 5

SCID Mouse Model Vascular Lesion Showing Mesenchymal Proliferation in the Expanded Intima



A. High-power view of a transplanted human artery with intimal expansion and a mild mononuclear infiltrate (bar). **B.** The same artery showing immunohistochemical stain for smooth muscle α-actin. Deposition of smooth muscle fibers in the abnormal expanded intimal layer (bar) is demonstrated. The positive staining within the infiltrating lymphocytes indicates the presence of cytolytic T-effector cells SCID indicates severe combined immunodeficient.

Reprinted with permission from Lorber MI et al. *Transplantation*. 1999;67:897-903.[27]

Available Immunosuppressive Therapies

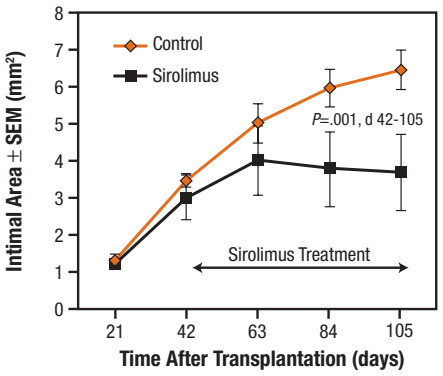
Currently, most kidney transplant recipients are maintained on a triple-drug regimen that includes an antiproliferative agent (often an antimetabolite), a steroid, and an antilymphocytic agent. In addition, induction with a monoclonal antibody has become a routine part of kidney transplantation. In recent years, mycophenolate mofetil has virtually replaced azathioprine as the antimetabolite of choice in the posttransplant setting.[32]

Calcineurin inhibitors, agents that interfere with transcription of interleukin IL-2 and related lymphokines necessary for activation and proliferation of T-cells, have revolutionized transplant immunosuppression since the early 1980s.[32,33]

The choices for immunosuppressive therapy expanded in 1998 with the Food and Drug Administration approval of sirolimus (rapamycin), the first of a new class of immunosuppressive agents that act downstream from calcineurin inhibitors and thus have a complementary mechanism of action (Figure 8, page 6).[32,33] Sirolimus remains the only TOR inhibitor available in the United States to date, although an analog, everolimus, is currently being studied in clinical trials.[31] In 2001, 21% of kidney transplant recipients were taking sirolimus for maintenance immunosuppression.[32] Sirolimus and everolimus inhibit mTOR (mammalian target of rapamycin) kinase, which in turn blocks Cdk2 and p70 S6 kinase, key enzymes in cell-cycle progression.[33-36] TOR inhibitors impede the proliferation of an array of cell types including vascular smooth muscle cells.[37] This antiproliferative activity is consistent with the prevention of intimal thickening discussed previously.[30,31]

Figure 6

Sirolimus-Arrested Vasculopathy Development in a Primate Model

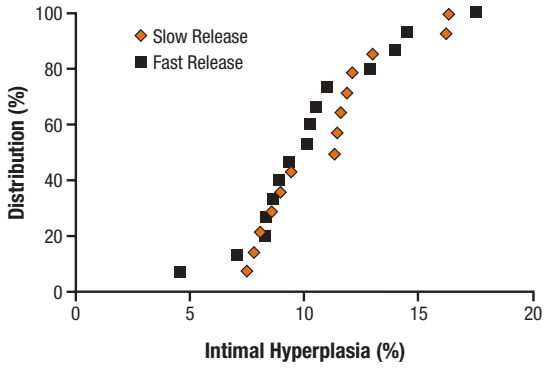


Mean intimal areas (IA) of the aortic allografts from untreated and sirolimus-treated monkeys assessed by serial intravascular ultrasound studies at 3-week intervals. Treatment with sirolimus was started at day 45 after analysis of IA on day 42 to confirm initial development of graft vascular disease in the walls of the allografts.

Adapted with permission from Ikonen TS et al. *Transplantation*. 2000; 70:969-975.[29]

Figure 7

Sirolimus–Coated Stents



Adapted with permission from Sousa JE et al. *Circulation*. 2001;103:192-195.[30]

Immunosuppression—Looking Forward

Recent results using these newer immunosuppressants suggest that it is now possible to develop safe and effective approaches with less reliance on the calcineurin inhibitor class of agents. Approaches using calcineurin inhibitor dose reduction[38] as well as those using calcineurin inhibitor elimination or even complete avoidance have been reported with high rates of success.[39]

Although the characteristics of individuals who may benefit most from each of these approaches remain speculative at this juncture, it seems apparent that each protocol approach may have advantages for different patient subpopulations.

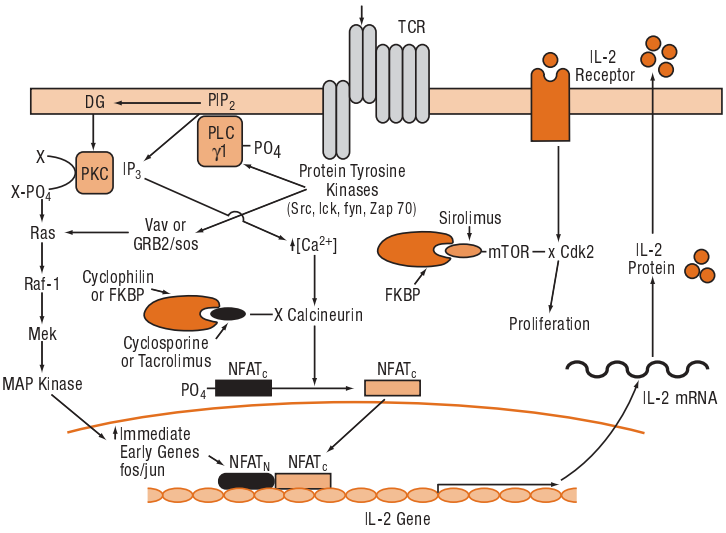
TOR-Inhibitors and Long-Term Graft Survival

The modification of calcineurin inhibitor–based therapies has been enhanced through the use of sirolimus. Since the clinical availability of sirolimus more than 5 years ago, physicians have expanded their experience base with this drug, and long-term clinical data are now available. Findings from multiple studies in kidney transplant recipients demonstrate that sirolimus in combination with other non–calcineurin inhibitors can provide a similar net state of immunosuppression as does cyclosporine or tacrolimus with superior renal function after a year or more of follow-up. These studies are summarized in Table 3, page 7. Results of these clinical trials indicate that sirolimus is a valuable addition to the immunosuppressive drug armamentarium and is a useful tool in the modification of calcineurin-based immunosuppressive regimens.

To evaluate the outcomes of patients taking sirolimus in drug avoidance protocols, Flechner et al compared the TOR inhibitor with cyclosporine in patients also receiving mycophenolate mofetil and prednisone after basiliximab

Figure 8

Mechanisms of Action of Cyclosporine, Tacrolimus, and Sirolimus



Adapted with permission from Pattison JM, Sibley RK, Krensky AM. Mechanisms of allograft rejection. In: Nielson EG, Couser WG, eds. *Immunologic Renal Diseases*. Philadelphia, Pa: Lippincott-Raven Publishers; 1997:331-354.[52]

induction.[39] To evaluate the outcomes of patients taking sirolimus in drug avoidance protocols, Flechner et al compared the TOR inhibitor with cyclosporine in patients also receiving mycophenolate mofetil and prednisone after basiliximab induction. At 1-year posttransplantation, there were no significant differences in patient or graft survival.[39] However, unpublished data suggest that, over the 3-year follow-up period, patients receiving the sirolimus-based regimen show better renal function and less evidence of chronic allograft nephropathy compared to the cyclosporine-treated group.[40]

These results are similar to findings in two earlier comparative studies of sirolimus and cyclosporine.[41,42] In these trials, although there was no significant difference in patient or graft survival or in the incidence of biopsy-proven acute rejection at 1-year posttransplantation,[41,42] elevated serum creatinine levels occurred in 39% of patients taking cyclosporine versus 18% of those taking sirolimus ($P<.05$). Thrombocytopenia and diarrhea were reported significantly more frequently in patients receiving sirolimus and mycophenolate mofetil, and hyperuremia, cytomegalovirus infection, and tremor occurred significantly more frequently in those receiving cyclosporine and mycophenolate mofetil.[42]

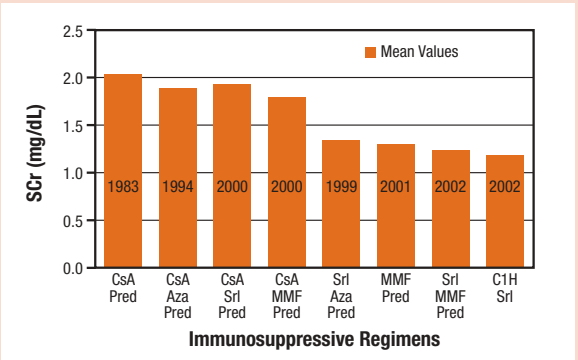
Sirolimus-based immunosuppression has also been used successfully in drug elimination protocols. In a recently reported trial of 470 primary and secondary kidney transplant recipients of both living- and deceased-donor kidneys, Kreis et al reported that elimination of cyclosporine with continued use of sirolimus resulted in significantly better renal function than did continued cyclosporine use (glomerular filtration rate [GFR], 59.4 mL/min vs 47.3 mL/min, respectively; $P<.001$) at 3 years posttransplantation. No significant difference in graft survival was observed.[43] One-year results of a tacrolimus elimination trial[44,45] and 2-year results of another cyclosporine elimination trial showed similar graft survival between treatment groups.[46]

Unpublished data from two groups using everolimus, in combination with low-dose cyclosporine, suggest that this regimen leads to low rates of biopsy-proven acute rejection at 1-year with good renal function, but long-term data are not yet available on these protocols.[47,48]

Overall, the TOR inhibitors have demonstrated a favorable safety profile. However, perhaps the most vexing problem in early phase III trials of sirolimus combined with cyclosporine was increasing serum creatinine levels. Because the nephrotoxicity of calcineurin inhibitors can be dose-limiting[33] and because the immunosuppressive action of sirolimus does not act via the calcineurin pathway, it was thought that combination therapy had the potential to improve efficacy with better renal function. In early studies, however, a small but significant increase in serum creatinine levels and reductions in GFR were reported for sirolimus plus cyclosporine regimens compared with azathioprine plus cyclosporine or cyclosporine alone.[49,50] As a result, combination therapy with sirolimus and calcineurin inhibitors may be less suitable as long-term maintenance therapy. As has been shown, sirolimus alone or in combination with other non–calcineurin inhibitors does not exhibit nephrotoxicity at doses that achieve necessary immunosuppression.[51] In fact, calculated GFR posttransplantation has been reported to improve with sirolimus treatment.[43] Of the various combinations of immunosuppressive agents that have been used to preserve long-term renal function, those using sirolimus in combination with other non–calcineurin inhibitors have consistently resulted in 1-year serum creatinine levels <1.5 mg/dL (Figure 9), supporting its usefulness and potential to improve long-term success posttransplantation.

Figure 9

One-Year Serum Creatinine Levels Are Consistently <1.5 mg/dL With Sirolimus in Combination With Other Non–Calcineurin Inhibitors



SCr indicates serum creatinine; CsA, cyclosporine; Pred, prednisone; Aza, azathioprine; Srl, sirolimus; MMF, mycophenolate mofetil; C1H, Campath-1H antibody (Anti-CD52).

Courtesy of S. Flechner.

Table 3

TOR Inhibitor Clinical Trials: Long-Term (≥12 Months) Results in Adult Kidney Transplant Recipients

Author (year)	Experimental Design	Outcomes
CNI Avoidance Studies		
Flechner et al* (*2002, 2004*)[39,40]	Randomized, prospective trial in primary kidney transplant recipients (N=61) SrI or CNI combined with basiliximab induction, MMF and steroid maintenance	**At 12 months:** No significant difference in patient or graft survival rates or in acute rejection rates **At 3 years:** No significant difference in patient or graft survival rates (acute rejection not measured)
Kreis et al (*2000*)[41]	Open-label trial in first deceased-donor kidney recipients (N=78) SrI (n=40) or CsA (n=38) combined with MMF 2 g/day and steroids	**At 12 months:** No significant difference in graft or patient survival or in incidence of biopsy-proven acute rejection Serum Cr increased in 18% of SrI patients and 39% of CsA patients ($P<.05$) Adverse events reported more commonly with: SrI = thrombocytopenia, diarrhea; CsA = hyperuricemia, CMV infection, tremor
Groth et al (*1999*)[42]	Randomized, open-label, multicenter study in first, deceased-donor kidney recipients (N=83) CsA (n=42) or SrI (n=41) in combination with azathioprine and steroids	**At 12 months:** No significant difference in patient or graft survival or in incidence of biopsy-proven acute rejection Serum Cr (µmol/L, mean ± SEM): CsA = 133.5 ± 7.7; SrI = 115.8 ± 8.9 (NS) GFR (mL/min, mean ± SEM): CsA = 58.7 ± 3.6; SrI = 69.5 ± 4.1 (NS)
CNI Elimination Studies		
Kreis et al (*2004*)[43]	Randomized, open-label, multicenter trial in primary, secondary, deceased-donor or living-donor kidney recipients (N=470) SrI 2 mg/day plus CsA and steroids for 3 months followed by randomization to either continued 3-drug therapy or CsA withdrawal and gradual SrI increases	**At 36 months:** Calculated GFR (mL/min): CsA + SrI + steroids = 47.3 SrI + steroids = 59.4 ($P<.001$) Slope of GFR (mL/min/y, mean ± SEM): CsA + SrI + steroids = - 3.04 ± 0.45 (95% CI, -3.93, -2.15) SrI + steroids = 0.83 ± 0.45 (95% CI, -0.056, -1.71) ($P<.001$) Graft survival rate (%): CsA + SrI + steroids = 85.1 SrI + steroids = 91.2 ($P<.052$) Nonsignificant increase in number of acute rejection episodes after randomization with SrI + steroids
Ciancio et al (*2004*)[44,45]	Randomized, long-term trial in HLA-mismatched deceased-donor or living-donor kidney recipients (N=150) SrI or MMF in tacrolimus elimination protocol compared with SrI in CsA elimination protocol	**At 12 months:** No significant difference in patient or graft survival Trend toward rising serum Cr levels in SrI plus CsA group Acute rejection rates were significantly higher in SrI/CsA elimination group ($P>.03$ vs other 2 groups combined)
Oberbauer (*2003*)[46]	Open-label study in primary or secondary renal allograft recipients with deceased or living donors (N = 525) SrI 2 mg/day plus CsA and steroids for 3 months followed by randomization to either continued 3-drug therapy or CsA withdrawal and gradual SrI increase	**At 24 months:** No statistical difference in patient or graft survival or in acute rejection rates after randomization or discontinuation of therapy between the 2 treatment groups Serum Cr (µmol/L): SrI + CsA + steroids =167 SrI + steroids = 128 ($P<.001$)

	CNI	SrI	*P*
6 months			
Serum CR (mg/dL)	1.74	1.29	.008
GFR (mL/min)	64.1	77.8	.006
12 months			
Serum Cr (mg/dL)	1.78	1.32	.004
GFR (mL/min)	61.1	81.1	.008
3 years			
Serum Cr (mg/dL)	1.79	1.33	.01
GFR (mL/min)	63.6	80.6	.01
Lothalamate measured GFR (mL/min)	49.2	60.6	.01
Banff-scored chronic allograft nephropathy (%)	78	37	.007

(continued on page 8)

Table 3 (continued)

TOR Inhibitor Clinical Trials: Long-Term (≥12 Months) Results in Adult Kidney Transplant Recipients

Author (year)	Experimental Design	Outcomes
CNI Reduced Exposure Studies		
Magee et al* (*2004*)[47]	Randomized, open-label, multicenter, 1-year trial in de novo renal transplant recipients (N=237) Evrl 1.5 mg/day or 3 mg/day in combination with steroids and reduced CsA exposure	**At 12 months:** No significant difference in composite of biopsy-proven acute rejection, graft loss, death, or loss to follow-up between the 2 treatment groups Serum Cr (µmol/L, mean): Evrl 1.5 mg = 140 Evrl 3 mg = 137 Cr clearance (mL/min, mean): Evrl 1.5 mg = 65 Evrl 3 mg = 64
Whelchal et al* (*2004*)[48]	Randomized, open-label, multicenter, 1-year trial in de novo renal transplant recipients (N = 256) Evrl 1.5 mg/day or 3 mg/day in combination with basiliximab, steroids, and reduced CsA exposure	**At 12 months:** No significant difference in composite of biopsy-proven acute rejection, graft loss, death, or loss to follow-up between the 2 treatment groups Serum Cr (µmol/L): Evrl 1.5 mg = 137 Evrl 3 mg = 136 Mean Cr clearance (mL/min): Evrl 1.5 mg = 67 Evrl 3 mg = 64
CNI + TOR Inhibitor Study		
MacDonald (*2001*)[49]	Randomized, placebo-controlled, Phase III, double-blind study in primary mismatched deceased-donor and living-donor kidney recipients (N=576) Srl 2 mg or 5 mg/day vs placebo combined with CsA and steroids	**At 12 months:** No significant difference in graft loss or death among the groups Incidence of acute rejection episodes was significantly reduced in both treatment groups
Kahan (*2000*)[50]	Randomized, multicenter study in primary HLA-mismatched deceased-donor or living-donor renal allografts that had initial graft function following transplantation (N=719) Srl 2 mg or 5 mg/day or azathioprine added to CsA plus steroids	**At 12 months:** Survival was similar for grafts and patients for all groups, and time to acute rejection was longer for the Srl-treated patients with decreased frequency of moderate to severe histologic grades of rejection episodes Serum Cr levels were significantly higher in the Srl-treatment groups, and mean Cr clearance was significantly lower

*Data presented at the American Transplant Congress 2004.

CNI indicates calcineurin inhibitor; Srl, sirolimus; MMF, mycophenolate mofetil; Cr, creatinine; GFR, glomerular filtration rate; CsA, cyclosporine; CMV, cytomegalovirus; SEM, standard error of the mean; NS, not significant; HLA, human leukocyte antigen; Evrl, everolimus.

Summary

Acute rejection can be well controlled with existing immunosuppressive therapies. However, a serious need for strategies that improve long-term graft survival remains. The understanding that protection from renal injury is critical to reaching this goal strongly suggests that modifying immunosuppressive therapies can result in a reduction in drug-induced nephrotoxicity. The availability of the TOR inhibitor sirolimus has facilitated development of regimens to reduce patient exposure to nephrotoxic calcineurin inhibitors. In calcineurin inhibitor–free combination therapy, sirolimus achieves successful immunosuppression with consistently better long-term graft function than do calcineurin-inhibitor–based regimens.

The next offering in this series of continuing medical education monographs will present case studies that illustrate appropriate management of kidney transplant recipients with differing needs for immunosuppression.

Modifiable and Nonmodifiable Donor and Recipient Factors as Targets for Preservation of Renal Function

CME Posttest and Evaluation

Release Date: October 2004 Expiration Date: October 31, 2005

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Posttest

1. Which of the following have consistently been shown to be negative prognostic indicators of graft survival?
   a. Delayed graft function (DGF)
   b. Acute rejection
   c. Serum creatinine values in the first 6 months
   d. None of the above
   e. All of the above
2. According to the Port algorithm, kidneys are considered acceptable for transplantation if the relative risk of graft loss is ≤1.7 (compared with conventional criteria donors) based on which combination of donor risk factors?
   a. Age, stroke death, history of hypertension, and elevated serum creatinine
   b. Age, cold ischemia time, stroke death, and elevated serum creatinine
   c. Age, cold ischemia time, history of hypertension, and elevated serum creatinine
   d. Age, cold ischemia time, stroke death, history of hypertension
   e. None of the above
3. Meier-Kriesche et al have found that at 5-years, graft survival rates for patients were _____% for those on dialysis >2 years time before transplantation and ____% for those on dialysis <6 months.
   a. 58%, 78%
   b. 58%, 29%
   c. 29%, 68%
   d. 68%, 78%
   e. 58%, 68%
4. Longer waiting time and complexity of HLA matching for African Americans contributes to which of the following?
   a. 10% lower graft survival rate compared with Caucasians
   b. Twofold greater incidence of DGF
   c. Increased incidence of chronic allograft rejection
   d. All of the above
   e. None of the above
5. Evidence suggesting that many of the risk factors for graft loss are associated with injury leading to diminished renal function includes:
   a. Discharge serum creatinine levels >2.5 mg/dL are a strong negative predictor of graft survival at 1-year posttransplantation, and elevated serum creatinine levels (>2.0 mg/dL) at 6 months more than doubled the risk of chronic allograft rejection.
   b. For kidney transplantations performed between 1988 and 1996 the relative hazard for graft failure was found to be 1.63 (95% CI 1.61-1.65; *P*<.0001) for each incremental increase of 1.0 mg/dL of serum creatinine at one year
   c. a and b
6. In a comparison of patients initially treated with cyclosporine and those initially treated with azathioprine, cyclosporine treatment led to significantly better graft survival rates for the first 3 years after kidney transplantation, but:
   a. Declined to a similar rate as azathioprine treatment by the third year.
   b. Continued to be significantly worse for as long as 10 years.
   c. By 10 years, the graft survival rates were similar regardless of initial treatment.
   d. Graft survival in the cyclosporine treatment group was significantly worse at the end of 10 years.
   e. Graft survival rates were similar to azathioprine at 3 years, 5 years and 10 years.
7. The distinctions between vascular and interstitial acute rejection are:
   a. Probably the result of the arterial wall being the first site to encounter immune system cells.
   b. Important because they are associated with very different responses to antirejection treatments and ultimately with graft survival.
   c. Associated with different outcomes because vascular rejection occurs in normal criteria donor kidneys and interstitial rejection occurs in extended criteria donor kidneys.
   d. Of little clinical consequence.
   e. None of the above
8. The TOR inhibitor sirolimus can:
   a. Abrogate alloimmune microvascular lesions in combination with cyclosporine in a SCID mouse model.
   b. Act synergistically with mycophenolate mofetil to inhibit vascular fibrous intimal thickening, allograft glomerulopathy, and interstitial fibrosis in an animal model.
   c. Elicit minimal neointimal proliferation in patients receiving sirolimus-coated stents during acute coronary syndromes.
   d. Arrest progression of allograft vascular disease in nonhuman primates.
   e. All of the above
9. Calcineurin inhibitors inhibit production of interleukin-2
   a. True
   b. False
10. Tacrolimus and sirolimus have similar mechanisms of action.
    a. True
    b. False
11. In a comparison of sirolimus with cyclosporine in patients also receiving mycophenolate mofetil and prednisone after basiliximab induction:
    a. Graft survival was significantly better with sirolimus than cyclosporine treatment at 1-year and 3-years posttransplantation.
    b. Graft and patient survival were both significantly better with cyclosporine treatment.
    c. Renal function was significantly better in the cyclosporine-based regimen over the 3-year follow-up.
    d. The percentage of patients with Banff-scored chronic allograft nephropathy in the sirolimus group was roughly half that of the cyclosporine group at 3 years posttransplantation.
    e. None of the above
12. In patients treated with sirolimus plus other non–calcineurin inhibitors:
    a. Calculated glomerular filtration rate (GFR) has been reported to consistently decline following transplantation but more slowly than with calcineurin inhibitor treatment.
    b. Calculated GFR has been reported to improve.
    c. 1-year serum creatinine levels >1.5 mg/dL are consistently observed.
    d. Mean calculated GFR decreases in association with histologically confirmed nephrotoxicity.
    e. None of the above
13. Early results indicate that everolimus given with low-dose cyclosporine achieves low rates of biopsy-proven acute rejection (approximately 18%) at 1-year.
    a. True
    b. False
14. In drug elimination or substitution protocols, particular drugs are specifically not used at all to avoid their toxic effects.
    a. True
    b. False

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Posttest Answer Key

1. a b c d e	3. a b c d e	5. a b c	7. a b c d e	9. a b	11. a b c d e	13. a b
2. a b c d e	4. a b c d e	6. a b c d e	8. a b c d e	10. a b	12. a b c d e	14. 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

4. The educational activity has enhanced my professional effectiveness and improved my ability to communicate with patients.
   ❑ Strongly Agree ❑ Agree ❑ Disagree ❑ Strongly Disagree ❑ N/A

5. The information presented was free of promotional or commercial bias.
   ❑ Agree ❑ Disagree

6. What changes will you make in your practice as a result of participating in this program?

   _____

   _____

7. Comments/suggestions regarding *this* material:

   _____

   _____

8. Recommendations for *future* presentations:

   _____

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Target Audience

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, participants will be able to describe the:

- Magnitude of the problem of length of waiting list for transplantation
- Modifiable donor and recipient related risk factors
- Non-modifiable risk factors
- Impact of vascular rejection and renal function on graft loss
- Impact of newly available immunosuppressive regimens on the preservation of long-term renal function

Term of Approval

Date of Original Release: October 2004

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