



Outcomes Using Reduced Calcineurin Inhibitors in Renal Transplantation

Expert Commentary by

Michael C. Chobanian, MD

Medical Director
Solid Organ Transplant Surgery
Dartmouth-Hitchcock Medical Center
Lebanon, New Hampshire

Medical Reviewer

Mark A. Gendreau, MD, MS

Senior Staff Physician
Lahey Clinic
Burlington, Massachusetts

**This activity is certified for CME, CEU,
CEPTC, CNE, and CCMC credit**

Release Date: April 2008

Expiration Date: April 30, 2009



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Faculty and Planning Committee

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Michael C. Chobanian, MD, *Medical Director,
Solid Organ Transplant Surgery,
Dartmouth-Hitchcock Medical Center,
Lebanon, New Hampshire*

Medical Reviewer

Mark A. Gendreau, MD, MS, *Senior Staff Physician,
Lahey Clinic, Burlington, Massachusetts*

Planning Committee

Tim I. Robinson, *President,
Millennium CME Institute, Inc., Hampton, New Hampshire*

Frank A. Gesek, PhD, RPh, *Clinical Affairs Specialist,
Millennium CME Institute, Inc., Hampton, New Hampshire*

Peter B. Lindgren, PhD, *Clinical Affairs Specialist,
Millennium CME Institute, Inc., Hampton, New Hampshire*

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Michael C. Chobanian, MD	Tim I. Robinson
Mark A. Gendreau, MD, MS	Jennifer Verbesey, MD
Frank A. Gesek, PhD, RPh	Abigail Zavod, MD
Peter B. Lindgren, PhD	

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Target Audience & Learning Objectives

This CME/CE-certified monograph is intended for renal transplant surgeons, transplant specialists, and community nephrologists

Upon completing this activity, you should be able to:

1. Discuss the benefits of early steroid withdrawal and replacement with sirolimus and mycophenolate mofetil to minimize calcineurin inhibitors in renal transplant recipients.
2. Compare the efficacy of alemtuzumab induction in conjunction with calcineurin inhibitor maintenance or calcineurin inhibitor-free therapy.
3. Examine low- and high-dose tacrolimus levels on rejection and adverse effects in renal transplant recipients.
4. Determine the impact of calcineurin inhibitor reduction on renal function and graft survival in renal transplant patients.

Instructions

The learner should read the learning objectives and review the activity in its entirety. After reviewing the material, the learner should complete the Activity Self-assessment Test consisting of a series of multiple-choice questions.

Upon successfully completing this activity as designed and achieving a passing score of 70% or higher on the Activity Self-assessment Test, participants will receive a continuing education credit letter awarding the appropriate credit and the Activity Self-assessment Test answers four to six weeks after the receipt of the registration and evaluation materials.

Estimated time to complete this CME/CE-certified monograph as designed is 1.0 hours.

Accreditation

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The International Transplant Nurses Society has applied to American Board of Transplant Coordinators (ABTC) for approval of CEPTC credits for transplant coordinators and to the American Association of Critical-Care Nurses (AACN) for Continuing nursing education credits (CEU's).

This CNE activity has been approved by American Board of Transplant Certification, an accredited approver of continuing nursing education for 1 Category 1 CEPTCs. Program reference number 3000-219.

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This program has been approved for 1 contact hour by CCMC or the Commission for Case Manager Certification.

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This CME-certified monograph is supported by an educational grant from Astellas Pharma US, Inc.

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Kidney transplantation is the treatment of choice for most patients with end-stage renal disease. The major challenges facing the effective management of patients in need of renal transplantation include increasing the availability of more organs for transplantation, designing more effective and less toxic immunosuppressive regimens, and prolonging long-term survival.¹⁻⁴

Although the calcineurin inhibitors remain the primary immunosuppression agents used for renal transplantation, other agents have recently been used in combination with calcineurin inhibitors or in some cases, replacements for calcineurin agents; over the last several years the rate of acute rejection and short-term survival has improved.⁵ However, the use of non-calcineurin therapy for immunosuppression and its impact on long-term outcomes remains unclear. Recent studies have focused on improving long-term graft and patient survival while maintaining graft function. The use of induction agents (antithymocyte globulin (ATG), basiliximab, daclizumab), mycophenolate mofetil, and sirolimus, has facilitated steroid and calcineurin inhibitor minimization or replacement regimens for kidney transplantation.⁶⁻¹⁰

The calcineurin inhibitors cyclosporine and tacrolimus are integral components of maintenance immunosuppressive therapy. Each of these agents are highly effective in reducing the incidence of acute rejection and prolonging graft and patient survival.¹¹⁻¹³ Survival is negatively impacted by cardiovascular disease, which is the leading cause of mortality among transplant recipients with functioning grafts.¹⁴ In addition to their potential nephrotoxic effects, calcineurin inhibitors also contribute to other adverse effects that include hypertension, dyslipidemia, and diabetes mellitus, and may position these patients for increased risk for adverse cardiovascular outcomes. Thus, some clinicians have advocated a diminished role for calcineurin inhibitors going forward, a position that remains highly controversial.

Mycophenolate mofetil is effective in preventing acute rejection after kidney transplantation when added to calcineurin-based regimens. Ojo et al¹⁵ assessed acute rejection in 66,774 patients that received mycophenolate mofetil or azathioprine and reported that patients that received mycophenolate mofetil had a 15.5% incidence of rejection compared with 24.7% in patients receiving azathioprine. The four year graft survival rate was 85.6% with mycophenolate mofetil compared with 81.9% ($P < 0.0001$) with azathioprine; the four year patient survival was 91.4% with mycophenolate mofetil and 89.9% with azathioprine ($P = 0.002$).¹⁵ Sirolimus is another agent that has been used to replace or reduce calcineurin inhibitor therapy.

In patients that received sirolimus in addition to cyclosporine and prednisone, acute rejection was significantly lower (24.7%) compared with those receiving placebo (41.5%).¹⁶ There is increased nephrotoxicity associated with sirolimus and calcineurin inhibitors compared with mycophenolate mofetil and calcineurin inhibitors; accumulated clinical and scientific data suggest that sirolimus has inherent nephrotoxicity that occurs differently from that of calcineurin inhibitors.^{17,18}

The rationale for induction agent use in immunosuppression is to provide intense immunosuppression in the early post-transplant period and avoid acute rejection. Induction therapy with antibodies is utilized for both steroid and calcineurin inhibitor-sparing protocols.¹⁹ Early steroid withdrawal (5 days post-transplant) among renal transplant recipients receiving basiliximab induction indicates that acute rejection is not significantly different among the steroid withdrawal group (20%) compared with the steroid treatment group (16%); patient and graft-survival was 100% in the steroid withdrawal group for the 12 month follow-up period.²⁰ Calcineurin inhibitor withdrawal regimens substituting mycophenolate mofetil or sirolimus for maintenance immunosuppression is intended to improve renal function without a significant increase in acute rejection.²¹⁻²³ Similarly, calcineurin inhibitor avoidance regimens have been utilized in transplant recipients at low immunological risk substituting antibody and steroid induction followed by immunosuppression with mycophenolate mofetil, sirolimus, and steroid taper.²⁴⁻²⁶

Recent large-scale studies such as the SYMPHONY and CAESAR studies provide evidence for regimens using low-dose calcineurin inhibitors along with mycophenolate mofetil to achieve a reasonable balance between renal function and prevention of acute rejection.^{25,27} The SYMPHONY study compared conventional doses of cyclosporine plus mycophenolate mofetil and steroids with three regimens that included daclizumab induction, mycophenolate mofetil, and steroids along with low-dose cyclosporine, low-dose tacrolimus, or low-dose sirolimus. At 12 months, the results indicated that GFR was significantly higher with the low-dose tacrolimus regimen compared with conventional- or low-dose cyclosporine or low-dose sirolimus.²³ Similarly, the CAESAR study showed that a combination of low-dose cyclosporine with mycophenolate mofetil and steroids resulted in equivalent acute rejection rates compared with higher dose cyclosporine regimens and is a safe and effective immunosuppressive regimen.²⁷ These studies provide evidence that calcineurin inhibitor reduction and use of adjunct agents do not increase acute rejection and decrease nephrotoxicity to preserve renal function.

This *Transplantation Forum Report*™ discusses the benefits of early steroid withdrawal and replacement with sirolimus and mycophenolate mofetil to minimize calcineurin inhibitors in renal transplant recipients. The efficacy of induction therapy in conjunction with reduced calcineurin inhibitor maintenance or calcineurin inhibitor-free therapy will be evaluated. The outcomes resulting from calcineurin inhibitor reduction on acute rejection as well as patient

and graft survival will also be assessed. For your added benefit, CME/CE credits accompany this monograph.

Calcineurin Inhibitor-minimization Strategies Using Mycophenolate Mofetil

Efforts to reduce or discontinue calcineurin inhibitors are being evaluated in order to decrease the toxicities associated with calcineurin inhibitor use. Mycophenolate mofetil is used as a calcineurin inhibitor- or steroid-sparing agent since it does not cause neurotoxicity or nephrotoxicity.⁵ Several clinical trials have demonstrated that mycophenolate mofetil neither impairs renal function nor increases the incidence of acute rejection.²⁸⁻³¹ Some studies have also evaluated the complete withdrawal of calcineurin inhibitors and shown stable renal function with only small increases in the rates of acute rejection.^{32,33}

A recent study by Pallardo and colleagues³⁴ evaluated calcineurin inhibitor minimization strategies in 213 renal transplant recipients. The patients in the study underwent calcineurin inhibitor minimization for various reasons by at least 20% (as decided by the investigator). The majority of patients were being treated with a calcineurin inhibitor (66.7% using tacrolimus and 33.3% using cyclosporine) combined with mycophenolate mofetil and steroids in the immediate post-transplant period. Calcineurin inhibitor reduction occurred while all patients had been receiving mycophenolate mofetil. The primary reasons for calcineurin inhibitor reduction or elimination in this cohort were nephrotoxicity (55.9%) and to reduce adverse effects (21.6%). Other reasons for calcineurin inhibitor reduction included concerns over new-onset diabetes, hyperlipidemia, hypertension, and neurotoxicity. The average time to calcineurin inhibitor reduction was 9.9 ± 11.8 months and the acute rejection rate during this interval was 9.4%. This study coincided with the start of calcineurin inhibitor reduction in previous prospective trials (ranging from 6 months to 1 year).²⁸⁻³¹ The mean target calcineurin inhibitor dose reduction was $41.4\% \pm 21.45\%$ for patients receiving tacrolimus and $28.6\% \pm 10\%$ in the patients receiving cyclosporine, which correlates to the 25–50% calcineurin inhibitor reduction range reported in other studies.²⁸⁻³¹ The time to reach this reduction was 18.1 ± 15.0 weeks for patients receiving tacrolimus and 17.7 ± 8.9 weeks for patients receiving cyclosporine.

The authors indicate that the data presented in this study is consistent with others reported in the literature. Generally, most of the studies start reduction within 6 to 12 months following transplantation. Further, some patients in this study were able to achieve complete withdrawal of calcineurin inhibitors with maintenance of renal function and only a slight increase in acute rejection episodes. This data indicates that mycophenolate mofetil-based immunosuppression in renal transplant patients does not significantly increase the rate of acute rejection episodes while allowing for a dose reduction of calcineurin inhibitors in patients who demonstrate nephrotoxicity or other adverse effects.³⁴

Calcineurin Inhibitor Reduction on Renal Function and Graft Survival Outcomes

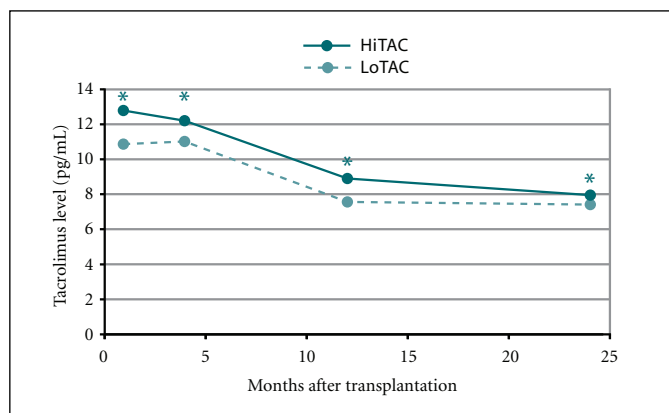
Calcineurin inhibitors are considered standard agents in the post-renal transplant management period. These agents are associated with nephrotoxicity, including renal interstitial fibrosis.^{35,36} A study by

Cosio and colleagues sought to determine the clinical and histological outcomes of reducing tacrolimus target blood levels in renal transplant recipients.³⁷

The change in drug levels (calculated 15% reduction) was an attempt to reduce the incidence of polyoma virus-associated nephropathy (PVAN) observed in these patients.³⁷ The analysis was performed on 575 adult renal transplant recipients, comparing data from two consecutive time periods—an earlier 2-year period using higher tacrolimus levels and a subsequent 2-year period using lower tacrolimus levels. All study patients received the same immunosuppressive medications: thymoglobulin induction, prednisone, mycophenolate mofetil, and tacrolimus. The group from the earlier time period (HiTAC group, $n = 245$) had the following tacrolimus levels: 12–15 ng/mL during the first month; 10–12 ng/mL from months 1–4; 8–10 ng/mL between months 4 and 12; and 6–8 ng/mL after the first year. Patients converted to the lower tacrolimus dosing from the later period (LoTAC group, $n = 330$) had the following tacrolimus levels: 10–12 ng/mL during the first month; 8–10 ng/mL from months 2–4; and 6–8 ng/mL thereafter. The other immunosuppressive medications were unchanged during this period. Graft function was measured by serum creatinine and direct measurement of GFR using radio labeled iothalamate clearance. The diagnosis of acute rejection was determined by histopathological analysis. The diagnosis of PVAN was confirmed by the presence of viral DNA in biopsies using *in situ* hybridization.

There were no significant differences between the HiTAC and LoTAC groups in demographic characteristics. Average tacrolimus levels measured at different time points are depicted in Figure 1 and indicate significant differences for serum levels between HiTAC and LoTAC groups at each of the time points. Compared to the HiTAC group, the LoTAC group had lower rates of PVAN (Figure 2), lower glucose levels, higher GFR levels, and a lower incidence and severity of renal interstitial fibrosis and tubular atrophy. The difference in PVAN after 1 year indicated a lower incidence in the LoTAC group (2.5% vs. 10.5%, $P < 0.0001$). Similarly, after 2 years, 12.7% of HiTAC and 3.6% of LoTAC patients developed PVAN. GFR measurements also favored the LoTAC group, with GFR measuring 59 ± 17 mL/min/1.73 m² vs. 52 ± 19 mL/min/1.73 m² ($P < 0.0001$). After 2 years, GFR values were still significantly higher in LoTAC

Figure 1. Average tacrolimus levels in the HiTAC (solid line) and LoTAC (dashed line) groups up to 24 months. Tacrolimus levels were significantly higher in HiTAC group than LoTAC group at 1, 4, and 12 months ($P < 0.001$) and 24 months ($P = 0.004$).^[adapted from 37]



compared to HiTAC patients (59 ± 18 mL/min/1.73 m² vs. 52 ± 17 mL/min/1.73 m², $P = 0.014$). Compared to the HiTAC group, fasting glucose levels were significantly lower in the LoTAC group throughout the first year, but after 2 years the difference was not statistically significant. In addition, renal biopsies demonstrated a lower incidence and severity of interstitial fibrosis in LoTAC patients after one year (45% vs. 67%; $P = 0.003$; Figure 3) and two years (49% vs. 75%; $P = 0.001$). Likewise, tubular atrophy was found to be lower in the LoTAC group at one year (66% vs. 82%; $P = 0.01$; Figure 3) and two years (90% vs. 67%; $P = 0.003$). Arteriolar hyalinosis was similar for both HiTAC and LoTAC groups and there were no significant differences in severity of transplant glomerulopathy or vasculopathy between the two treatment groups. The incidence and severity of acute rejection was similar between both groups.

Figure 2. Kaplan-Meier plots of the cumulative incidence of PVAN in HiTAC (dashed line) and LoTAC (solid line) patients (log rank, $P = 0.0007$). [adapted from 37]

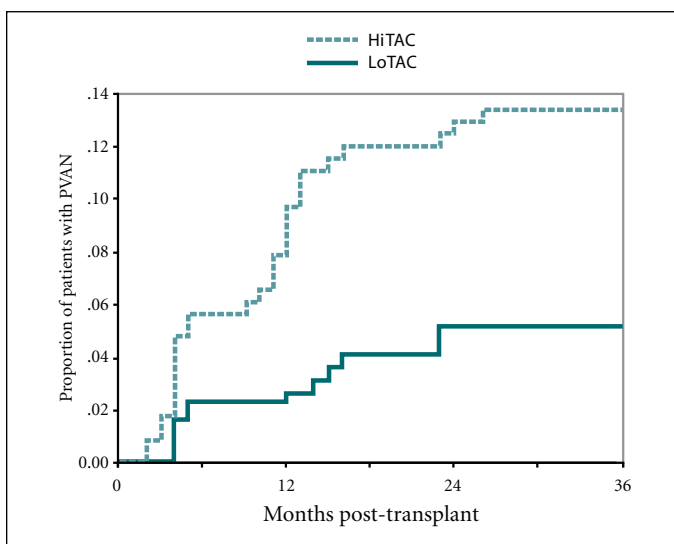
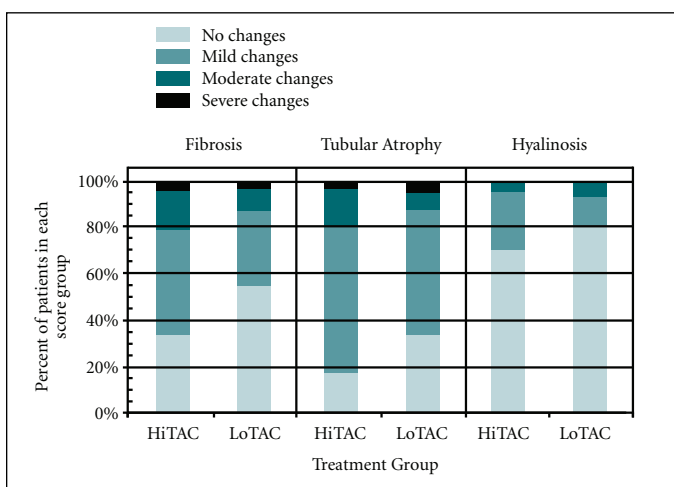


Figure 3. Severity of interstitial fibrosis, tubular atrophy, and arteriolar hyalinosis in one-year biopsies from HiTAC and LoTAC treatment groups. Open bars indicate no changes, light bars indicate mild changes, darker bars denote moderate changes, and black bars depict severe changes. [adapted from 37]

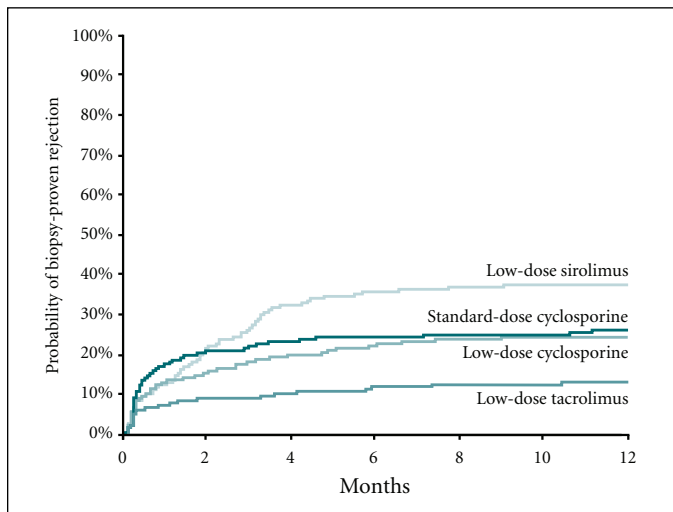


The authors' intent was to lower tacrolimus levels in an effort to reduce the incidence of PVAN. The results show that with a relatively modest reduction in tacrolimus levels there is a 72% reduction in the incidence of PVAN. The incidence of PVAN in kidney transplant recipients is primarily linked to the use of immunosuppressive drugs. Although the incidence is not linked to a specific immunosuppressive agent, it is more likely linked to overall immunosuppression and immunologic status of the recipient prior to transplantation.³⁷ Further, the incidence and severity of acute rejection did not change significantly with the implementation of the lower dosing of tacrolimus. However, the use of biopsies to assess histologic changes showed that tacrolimus contributes significantly to the development of interstitial fibrosis and tubular atrophy during the first year of transplantation. The severity of these changes appears to be related to calcineurin inhibitor drug levels.³⁸ Although these studies assessed changes in the early dosing of tacrolimus, less is known about maintenance dosing of calcineurin inhibitors after the first year.

Another recent study also evaluated the impact of calcineurin inhibitor reduction on renal function and graft survival in renal transplant patients.²³ This study was a 12-month prospective study designed to evaluate the efficacy and toxic effects of four different immunosuppressive regimens. The results showed that a regimen consisting of daclizumab, mycophenolate mofetil, and corticosteroids in combination with low-dose tacrolimus was more beneficial in terms of renal function, allograft survival, and acute rejection rates compared with other study regimens. A total of 1645 renal transplant recipients were included in the study and randomly assigned to one of the following four regimens: 1.) standard-dose cyclosporine, MMF, and corticosteroids; 2.) daclizumab induction, MMF, corticosteroids and low-dose cyclosporine; 3.) daclizumab induction, MMF, corticosteroids and low-dose tacrolimus; and 4.) daclizumab induction, MMF, corticosteroids and low-dose sirolimus. The primary endpoint in the study was renal function at 12 months post-transplantation determined by GFR using the Cockcroft-Gault formula. Secondary end points included allograft survival and acute rejection.²³

The regimen that included low-dose tacrolimus resulted in overall maintenance of renal function, improved graft survival, and decreased acute rejection compared with the other three regimens. The mean calculated GFR was significantly higher in patients receiving low-dose tacrolimus (65.4 mL/min), compared to standard dose cyclosporine (57.1 mL/min), low-dose cyclosporine (59.4 mL/min), or low-dose sirolimus (56.7 mL/min). Also, the rate of biopsy-proven acute rejection at 12 months favored the low-dose tacrolimus regimen (12.3%), compared to standard-dose cyclosporine (25.8%), low-dose cyclosporine (24%), or low-dose sirolimus (37.2%) (Figure 4). Allograft survival was significantly different among the 4 groups ($P = 0.02$), with the highest survival observed in the low-dose tacrolimus group (94.2%), followed by the low-dose cyclosporine group (93.1%), the standard-dose cyclosporine group (89.3%), and the low-dose sirolimus group (89.3%). Treatment failure was lowest in the low-dose tacrolimus group (12.2%) and highest in the low-dose sirolimus group (35.8%, $P < 0.001$). Serious adverse events were more frequent in the low-dose sirolimus group than in the other groups (53.2% vs. a range of 43.4 to 44.3%), although the proportion of patients in each group with at least one adverse event during treatment was similar (86.3% to 90.5%).

Figure 4. Cumulative probability of biopsy-proven acute rejection among four immunosuppressive regimens in renal transplant recipients. [adapted from 23]



Early Steroid Withdrawal and Replacement with Sirolimus and Mycophenolate Mofetil to Minimize Calcineurin Inhibitors

Chronic immunosuppressive therapy after kidney transplantation is important in preserving long-term graft and patient survival. Minimization of adverse effects from chronic immunosuppression is also crucial. Maintenance immunosuppression with corticosteroids was once thought to be required for preservation of graft survival. However, due to the advent of newer immunosuppressive therapies in recent years and the well-known serious side effects of corticosteroids, the gradual elimination of steroids from post-transplant immunosuppressive maintenance regimens is becoming more common. The side effects of steroids include osteoporosis, weight gain, myopathy, cataracts, gastric ulcer disease and glaucoma. Notably, long-term use of steroids also increases the risk of cardiovascular disease by promoting glucose intolerance, hypertension, and hyperlipidemia.³⁹⁻⁴¹ Thus, eliminating steroids and these adverse effects may improve patient survival. The challenge of eliminating steroids while maintaining graft function is currently under investigation. Several studies assessing late steroid withdrawal (more than three months) after renal transplantation showed increased risks of acute rejection.⁴²⁻⁴⁵ In contrast, several studies evaluating early rapid elimination of steroids showed excellent patient and graft survival with no increased incidence of acute rejection.⁴⁶⁻⁴⁸ The most recent of these studies by Matas and colleagues⁴⁹ demonstrated that early discontinuation of prednisone did not increase acute rejection rates, allograft dysfunction, or graft loss when compared to historical controls. Thus, the success of eliminating steroids from an immunosuppressive regimen may depend both on the timing of the steroid withdrawal and the efficacy of the remaining immunosuppressives in the regimen after withdrawal.

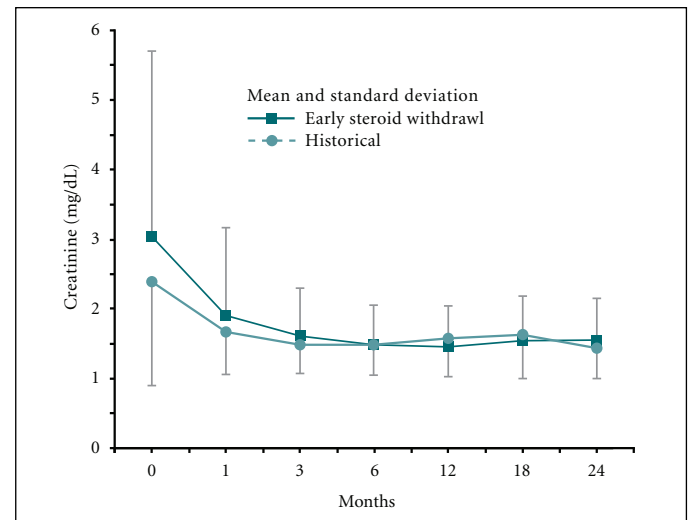
A recent retrospective study by Jaber and colleagues evaluated the outcomes of early steroid withdrawal in renal transplant recipients treated with a calcineurin inhibitor-minimization protocol.⁵⁰ The study included 84 kidney transplant recipients (61 deceased donors and 23 living donors) who underwent early steroid withdrawal.

Steroids were initiated intraoperatively and rapidly tapered and discontinued post-operatively by day 6. The immunosuppressive regimen for this group consisted of thymoglobulin antibody induction for 5 days and prednisone administered intraoperatively followed by a rapid taper over the next 6 days. Maintenance therapy included a calcineurin inhibitor-minimization protocol that consisted of sirolimus and mycophenolate mofetil-based immunosuppression. Tacrolimus and mycophenolate mofetil were initiated on the day of transplantation, and sirolimus was initiated post-operatively on day 6 coincident with the discontinuation of steroids. Clinical outcomes from the early steroid withdrawal group were compared to a group of historical controls (n = 50), who were kidney recipients at the same medical center in previous years. The immunotherapy regimen in this control group included selective thymoglobulin induction only in high-risk recipients and maintenance sirolimus, tacrolimus, and prednisone, which was continued throughout treatment.⁵⁰

The results for the early steroid withdrawal group indicated excellent 2.5-year actuarial patient survival (97%), graft survival (93%), and acute rejection-free graft survival (89%). Compared to historical controls, the early steroid withdrawal cohort had comparable graft survival, graft function, acute rejection-free survival, and significantly better patient actuarial survival ($P = 0.048$). Renal function, as assessed by mean serum creatinine, remained stable over time (1.5 ± 0.6 mg/dL at one year and 1.5 ± 0.6 mg/dL at two years; Figure 5). Hematologic complications such as anemia and leukopenia were frequent, but were aggressively managed and most cases resolved. Complications with post-transplant wound healing were present with both groups, although the historical control group had a significantly higher rate than the early steroid withdrawal group (18% vs. 5%; $P = 0.016$).⁵⁰

Beneficial effects for cardiovascular risk factors such as weight gain, hypertension, hyperlipidemia, and new-onset diabetes mellitus were observed among recipients who had early steroid withdrawal. The recipients with early steroid withdrawal had significantly less weight gain than the historical controls at both 6 months and 12 months, with a difference in weight gain of 1.5 kg for the early steroid

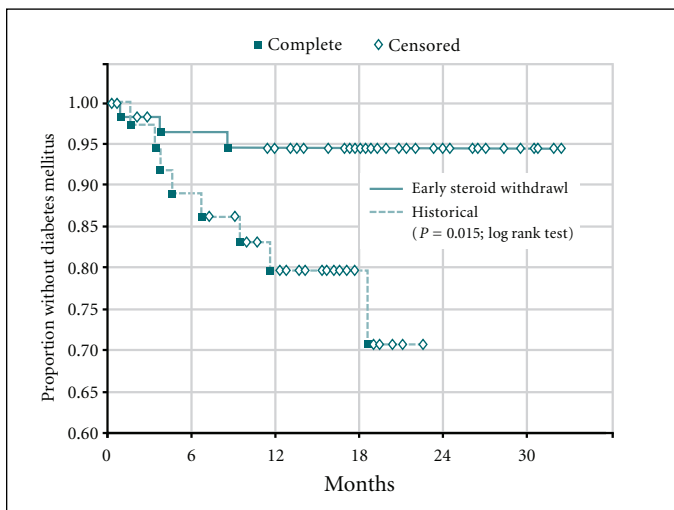
Figure 5. Comparison of serum creatinine levels for early steroid withdrawal patients (n = 84) and historical controls (n = 50). Data points indicate mean \pm SD; no significant difference was detected between the treatment groups. [adapted from 50]



withdrawal group and 5.2 kg for the control group after 1 year ($P = 0.024$). Discontinuation of steroids also significantly reduced the incidence of developing new-onset diabetes mellitus (5% early steroid withdrawal vs. 21% control; $P = 0.015$; Figure 6). Blood pressure control was assessed by comparing the number of antihypertensive drugs taken by recipients over time. As time progressed, the average number of antihypertensive agents for the last day of follow-up (21–22 months) was significantly higher in patients with steroid maintenance compared to those with steroid withdrawal (1.38 drugs vs. 1.86 drugs; $P = 0.008$). The mean change in required antihypertensive drugs per patient favored the early steroid withdrawal group (-0.52 ± 1.03 drugs/patient vs. $+0.34 \pm 0.92$ drugs/patient). Furthermore, compared with their pre-transplant requirements, 48% of steroid maintenance patients compared to 10% of early steroid withdrawal patients had an increase in ≥ 1 antihypertensive drug. Hyperlipidemia, which was analyzed between the 2 groups by assessing the change in the number of required anti-lipid agents from baseline, showed a significantly higher number of agents for the historical controls ($+0.66 \pm 0.63$ drugs/patient) compared to the early steroid withdrawal group ($+0.22 \pm 0.51$ drugs/patient) assessed on the last day of follow-up ($P < 0.001$). Accordingly, the mean cholesterol levels in the early steroid withdrawal group were lower than those observed for the control group despite less anti-lipid agents used in the early steroid withdrawal group.⁵⁰

The authors conclude from this study that early steroid withdrawal using thymoglobulin induction followed by a calcineurin inhibitor-minimization protocol of maintenance sirolimus and mycophenolate mofetil is associated with excellent patient and graft survival. Further, they report acceptable rates of rejection and reduced side effects that are observed with steroids including cardiovascular risk factors. Cardiovascular risk factors such as hypertension, hyperlipidemia, and new onset diabetes were significantly lower in the early withdrawal group. This study provides compelling evidence that early steroid withdrawal combined with calcineurin inhibitor-reduced immunosuppression in renal transplant recipients could effectively decrease steroid-related adverse effects, decrease cardiovascular disease risk factors, and improve patient survival without compromising graft function.

Figure 6. Comparison of the development of new-onset diabetes mellitus in the early steroid withdrawal group compared with controls. [adapted from 50]



Efficacy of Alemtuzumab Induction in Renal Transplantation

Alemtuzumab is a humanized monoclonal antibody directed against CD52, a glycoprotein expressed on circulating mononuclear cells.⁵¹ Although originally approved for treatment of chronic lymphocytic leukemia, alemtuzumab has been increasingly used for induction therapy in renal transplant recipients. Inducing lymphocyte depletion perioperatively with antilymphocyte antibodies is one strategy used to delay calcineurin inhibitor administration and reduce acute nephrotoxicity resulting from calcineurin inhibitors. Alemtuzumab induction has been used in several studies with various regimens including low-dose calcineurin inhibitors, no calcineurin inhibitors, and no steroids, with comparable graft survival to conventional protocols. However, many of these studies included small groups of study participants or short observation periods with results indicating variable acute rejection rates.^{52–55} The study by Vathsala et al. showed that alemtuzumab is an effective induction agent that permits low-dose steroid-free immunosuppression.⁵⁶ A second study by Ciancio et al. showed that 80% of patients receiving alemtuzumab remained steroid-free at 1 year following transplantation with lower levels of tacrolimus and no difference in other adverse events.⁵⁷ Unfortunately, it is difficult to assess long-term outcomes from these studies due to small sample sizes and a short duration of follow-up.

Recently Huang and colleagues⁵⁸ conducted a large retrospective analysis of deceased donor kidney transplantation using the Organ Procurement and Transplantation Network (OPTN)/United Network for Organ Sharing (UNOS) database to determine clinical outcomes associated with alemtuzumab induction. They compared alemtuzumab induction with no antibody induction, antithymocyte globulin (ATG) induction, and interleukin-2 receptor antagonist (basiliximab or daclizumab) induction. They also assessed outcomes in relation to common maintenance regimens, including calcineurin inhibitor-free protocols compared to triple immunosuppression.

A total of 14,362 patients were included in the analysis, including those who received no induction ($n = 4364$), ATG ($n = 4930$), interleukin-2 receptor antagonists (IL-2RAs, basiliximab or daclizumab) ($n = 4378$), and alemtuzumab ($n = 690$). This study reported that alemtuzumab induction was associated with a lower rate of acute rejection (2.3%) during the initial hospital stay compared with transplant recipients that received no antibody induction (7.6%), ATG (3.4%), or induction by IL-2RA (4.8%, $P < 0.001$). At 6 months post-transplant, the incidence of acute rejection was similar among patients receiving alemtuzumab, no induction, ATG, or IL-2RAs. At 1 year, the cumulative incidence of acute rejection with alemtuzumab induction surpassed that of no antibody induction, ATG, and IL-2RAs, respectively (19.2% vs. 14.8% vs. 10.2% vs. 13.0%; $P < 0.001$).

The graft survival rate in the alemtuzumab induction group was significantly lower than observed for the IL-2RA group ($P = 0.01$; Figure 7A). There was a sharp decline in alemtuzumab induction beginning 6 months post-transplant that continued past 24 months. Using multivariate analysis it was determined that no induction (RR: 0.76; $P = 0.002$), ATG (RR: 0.52; $P < 0.01$), and IL-2RA induction (RR: 0.66; $P < 0.001$) were each independently associated with a decreased risk for acute rejection compared with alemtuzumab.

This study also evaluated the effect of maintenance immunosuppression on graft outcomes in alemtuzumab recipients. The most common regimen (59.6%) consisted of a calcineurin inhibitor, mycophenolate mofetil, and steroids. Of the calcineurin inhibitor recipients, 65.9% were maintained on tacrolimus and 34.1% on cyclosporine. A total of 82 (11.9%) alemtuzumab patients were placed on a calcineurin-free immunosuppression regimen consisting of mycophenolate mofetil and steroids. Of these patients, 52.4% remained calcineurin inhibitor-free for 6 months with 26.8% then started on tacrolimus and 13.4% on cyclosporine. Graft and rejection-free survival for the various maintenance regimens is shown in Figure 8. The results indicate that patients discharged on calcineurin inhibitors had superior graft survival compared with those on calcineurin inhibitor-free regimens (tacrolimus/mycophenolate mofetil/steroids $P < 0.001$; cyclosporine/mycophenolate mofetil/steroids $P = 0.007$). Further, a comparison of patients maintained on tacrolimus/mycophenolate mofetil/steroids had superior graft survival rates compared with patients maintained on cyclosporine/mycophenolate mofetil/steroids ($P = 0.03$). Similarly, patients receiving calcineurin inhibitors demonstrated significantly better rejection-free survival compared to those on calcineurin-free protocols (tacrolimus/mycophenolate mofetil/steroids $P < 0.001$; cyclosporine/mycophenolate mofetil/steroids $P = 0.006$). Rejection-free survival

rates were similar for those treated with tacrolimus or cyclosporine ($P = 0.59$).

The authors conclude that alemtuzumab induction results in reduced acute rejection rates compared with ATG, IL-2RA, or no induction in the immediate post-transplant phase. Unfortunately this benefit was not sustained as evident at 6 month post-transplant and at 1 year alemtuzumab induction resulted in a significantly higher rate than observed with ATG, IL-2RA, or no induction. Further, in patients that were administered alemtuzumab induction and not maintained on calcineurin inhibitors, rejection-free and graft survival was reduced compared to those maintained on calcineurin inhibitors. These findings stress the need for further studies to assess long-term graft outcomes using alemtuzumab induction and to determine factors that can guide appropriate selection of maintenance immunosuppression regimens.

Conclusion

In summary, renal transplantation is the treatment of choice for patients with kidney failure. Effective management of renal transplant recipients includes implementing immunosuppressive regimens that are effective with a minimum of adverse effects. Calcineurin

Figure 7. Graft survival and rejection-free survival according to type of induction. [adapted from58]

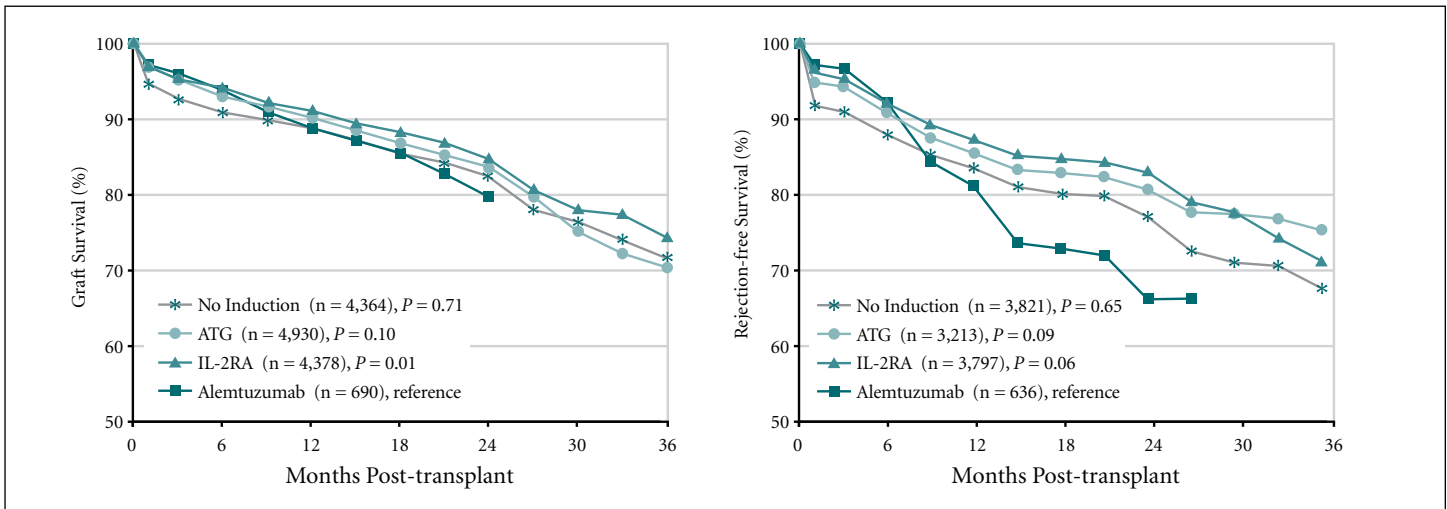
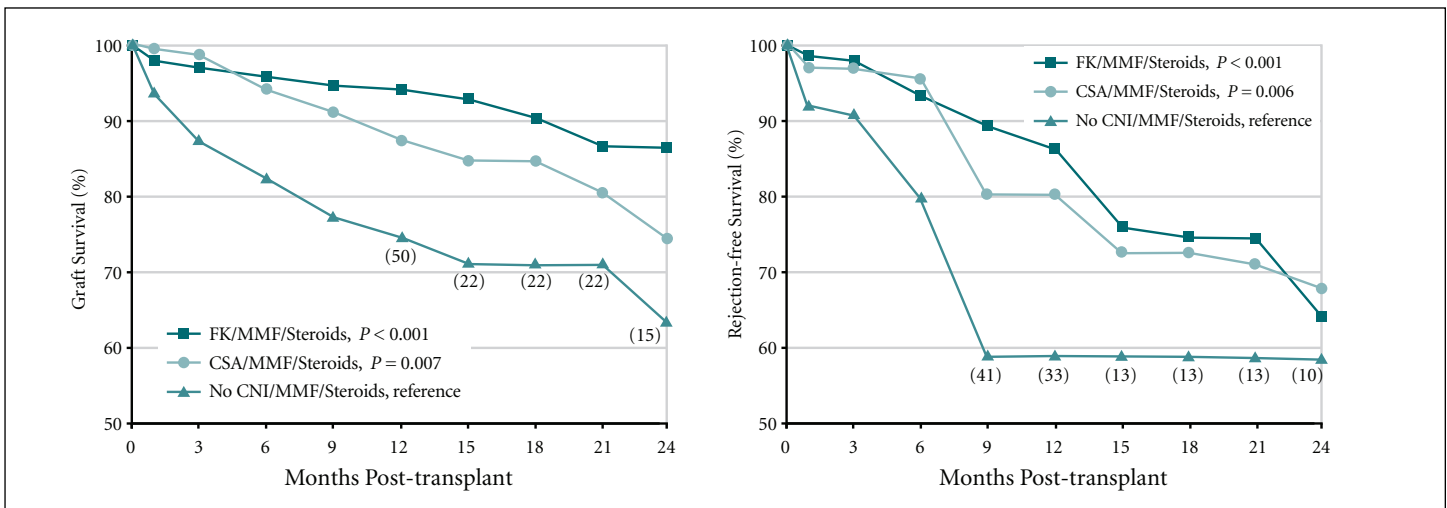


Figure 8. Effect of maintenance immunosuppression regimens on graft survival in renal transplant recipients receiving alemtuzumab induction. [adapted from58]



inhibitor-based immunosuppression has become an integral component of post-transplant management as they are highly effective in reducing acute rejection and prolonging patient survival. Unfortunately adverse effects such as nephrotoxicity have prompted investigators to consider minimizing calcineurin inhibitor doses or implementing alternative agents. In recent years there has been a shift in treatment focus from preventing acute rejection to aggressive management of long-term comorbidities. No study to date has adequately addressed outcomes with minimization of immunosuppression for more than a year or so. The optimal immunosuppressive

regimen post-renal transplantation has not yet been established, thus continued efforts to evaluate immunosuppressive regimens is still warranted for this patient population. Studies using mycophenolate mofetil-based immunosuppression do not increase acute rejection and allow a dose reduction in calcineurin inhibitors. Early steroid withdrawal or avoidance indicates excellent graft and patient survival and reduction of cardiovascular risk factors although exact timing of withdrawal for benefit has not been established. Finally, recent studies show promising results with induction agents coupled with mycophenolate mofetil and reduced calcineurin dosing.

References

- Bestard O, Cruzado JM, Grinyó JM. Calcineurin-inhibitor-sparing immunosuppressive protocols. *Transplant Proc.* 2005;37:3729-3732.
- Guerra G, Srinivas TR, Meier-Kriesche HU. Calcineurin inhibitor-free immunosuppression in kidney transplantation. *Transpl Int.* 2007;20:813-827.
- Créput C, Blandin F, Deroué B et al. Long-term effects of calcineurin inhibitor conversion to mycophenolate mofetil on renal function after liver transplantation. *Liver Transpl.* 2007;13:1004-1010.
- Flechner SM. Minimizing calcineurin inhibitor drugs in renal transplantation. *Transplant Proc.* 2003;35(3 Suppl):118S-121S.
- Flechner SM, Kobashigawa J, Klintmalm G. Calcineurin inhibitor-sparing regimens in solid organ transplantation: focus on improving renal function and nephrotoxicity. *Clin Transplant.* 2008;22:1-15.
- Hardinger KL, Schnitzler MA, Miller B et al. Five-year follow up of thymoglobulin versus ATGAM induction in adult renal transplantation. *Transplantation.* 2004;78:136-141.
- Lawen JG, Davies EA, Mourad G, et al. Randomized double-blind study of immunoprophylaxis with basiliximab, a chimeric anti-interleukin-2 receptor monoclonal antibody, in combination with mycophenolate mofetil-containing triple therapy in renal transplantation. *Transplantation.* 2003;75:37-43.
- Adu D, Cockwell P, Ives NJ, Shaw J, Wheatley K. Interleukin-2 receptor monoclonal antibodies in renal transplantation: meta-analysis of randomised trials. *BMJ.* 2003;326:789-794.
- Rostaing L, Cantarovich D, Mourad G et al. Corticosteroid-free immunosuppression with tacrolimus, mycophenolate mofetil, and daclizumab induction in renal transplantation. *Transplantation.* 2005;79:807-814.
- Ciancio G, Burke GW, Gaynor JJ et al. A randomized trial of three renal transplant induction antibodies: early comparison of tacrolimus, mycophenolate mofetil, and steroid dosing, and newer immune-monitoring. *Transplantation.* 2005;80:457-465.
- Pirsch JD, Miller J, Deierhoi MH et al. A comparison of tacrolimus (FK506) and cyclosporine for immunosuppression after cadaveric renal transplantation. FK506 Kidney Transplant Study Group. *Transplantation.* 1997; 63: 977-983.
- Vincenti F, Jensik SC, Filo RS et al. A long-term comparison of tacrolimus (FK506) and cyclosporine in kidney transplantation: evidence for improved allograft survival at five years. *Transplantation.* 2002; 73: 775-782.
- Mendez JR, Gonwa T, Yang HC, et al; Prograf Study Group. A prospective, randomized trial of tacrolimus in combination with sirolimus or mycophenolate mofetil in kidney transplantation: results at 1 year. *Transplantation.* 2005; 80: 303-309.
- Pascual M, Theruvath T, Kawai T et al. Strategies to improve long-term outcomes after renal transplantation. *N Engl J Med.* 2002; 346: 580-590.
- Ojo AO, Meier-Kriesche HU, Hanson JA et al. Mycophenolate mofetil reduces late renal allograft loss independent of acute rejection. *Transplantation.* 2000;69:2405-2409.
- MacDonald AS; RAPAMUNE Global Study Group. A worldwide, phase III, randomized, controlled, safety and efficacy study of a sirolimus/cyclosporine regimen for prevention of acute rejection in recipients of primary mismatched renal allografts. *Transplantation.* 2001;71:271-280.
- Meier-Kriesche HU, Steffen BJ, Chu AH et al. Sirolimus with neoral versus mycophenolate mofetil with neoral is associated with decreased renal allograft survival. *Am J Transplant.* 2004;4:2058-2066.
- Meier-Kriesche HU, Schold JD, Srinivas TR, Howard RJ, Fujita S, Kaplan B. Sirolimus in combination with tacrolimus is associated with worse renal allograft survival compared to mycophenolate mofetil combined with tacrolimus. *Am J Transplant.* 2005;5:2273-2280.
- Vincenti F, de Andrés A, Becker T et al. Interleukin-2 receptor antagonist induction in modern immunosuppression regimens for renal transplant recipients. *Transpl Int.* 2006;19:446-457.
- Vincenti F, Monaco A, Grinyó J, Kinkhabwala M, Roza A. Multicenter randomized prospective trial of steroid withdrawal in renal transplant recipients receiving basiliximab, cyclosporine microemulsion and mycophenolate mofetil. *Am J Transplant.* 2003;3:306-311.
- Hazzan M, Buob D, Labalette M et al. Assessment of the risk of chronic allograft dysfunction after renal transplantation in a randomized cyclosporine withdrawal trial. *Transplantation.* 2006;82:657-662.
- Abramowicz D, Del Carmen Rial M, Vitko S et al. Cyclosporine withdrawal from a mycophenolate mofetil-containing immunosuppressive regimen: results of a five-year, prospective, randomized study. *J Am Soc Nephrol.* 2005;16:2234-2240.
- Ekberg H, Tedesco-Silva H, Demirbas A, et al. Reduced exposure to calcineurin inhibitors in renal transplantation. *N Engl J Med.* 2007;357:2562-2575.
- Flechner SM, Kurian SM, Solez K et al. De novo kidney transplantation without use of calcineurin inhibitors preserves renal structure and function at two years. *Am J Transplant.* 2004;4:1776-1785.
- Flechner SM, Goldfarb D, Solez K et al. Kidney transplantation with sirolimus and mycophenolate mofetil-based immunosuppression: 5-year results of a randomized prospective trial compared to calcineurin inhibitor drugs. *Transplantation.* 2007;83:883-892.
- Grinyó JM, Cruzado JM. Mycophenolate mofetil and sirolimus combination in renal transplantation. *Am J Transplant.* 2006;6:1991-1999.
- Ekberg H, Grinyó J, Nashan B et al. Cyclosporine sparing with mycophenolate mofetil, daclizumab and corticosteroids in renal allograft recipients: the CAESAR Study. *Am J Transplant.* 2007;7:560-570.
- Hueso M, Bover J, Seron D, et al. Low-dose cyclosporine and mycophenolate mofetil in renal allograft recipients with sub-optimal renal function. *Transplantation.* 1998;66:1727-1731.
- Schrama YC, Joles JA, and van Tol A, et al. Conversion to mycophenolate mofetil in conjunction with stepwise withdrawal of cyclosporine in stable renal transplant recipients. *Transplantation.* 2000;69:376-383.
- Weir MR, Ward MT, Blahut SA, et al. Long-term impact of discontinued or reduced calcineurin inhibitor in patients with chronic allograft nephropathy. *Kidney Int.* 2001;59: 1567-1573.
- Pascual M, Curtis J, Delmonico FL, et al. A prospective, randomized clinical trial of cyclosporine reduction in stable patients greater than 12 months after renal transplantation. *Transplantation.* 2003;75: 1501-1505.
- Abramowicz D, Manas D, Lao M, et al. and Cyclosporine Withdrawal Study Group. Cyclosporine withdrawal from a mycophenolate mofetil-containing immunosuppressive regimen in stable kidney transplant recipients: a randomized controlled study. *Transplantation.* 2002;74: 1725-1734.
- Dudley C, Pohanka E, Riad H, et al. and Mycophenolate Mofetil Creeping Creatinine Study Group. Mycophenolate mofetil substitution for cyclosporine A in renal transplant recipients with chronic progressive allograft dysfunction: the "creeping creatinine" study. *Transplantation.* 2005;79: 466-75.
- Pallardo LM, Oppenheim F, Guirado L, Conesa J, et al. Calcineurin inhibitor reduction based on maintenance immunosuppression with mycophenolate mofetil in renal transplant patients: POP study. *Transpl Proceedings.* 2007;39:2187-2189.
- Okamoto M, Akioka K, Ushigome H et al. Ten-year protocol biopsy findings of renal allografts in the calcineurin inhibitor era. *Clin Transplant.* 2006;20:16-19.
- Chapman JR, O'Connell PJ, Nankivell BJ. Chronic renal allograft dysfunction. *J Am Soc Nephrol.* 2005;16:3015-3026.
- Cosio FG, Amer H, Grande JP, Larson TS, et al. Comparison of low versus high tacrolimus levels in kidney transplantation: assessment of efficacy by protocol biopsies. *Transplantation.* 2007;83:411-416.
- Chapman JR. Longitudinal analysis of chronic allograft nephropathy: clinicopathologic correlations. *Kidney Int Suppl.* 2005;99:S108-S112.
- Fryer JR, Granger DK, Levanthal JR et al. Steroid-related complications in the cyclosporine era. *Clin Transplant.* 1994;8:224-229.
- Schacke H, Docke WD, Asadullah K. Mechanisms involved in the side effects of glucocorticoids. *Pharmacol Ther.* 2002;96:23-43.
- Rhen T, Cidlowski JA. Antiinflammatory action of glucocorticoids - new mechanisms for old drugs. *N Engl J Med.* 2005;353:1711-1123.
- Hricik DE, O-Toole MA, Schulak JA, et al. Steroid-free immunosuppression in cyclosporine-treated renal transplant recipients: a meta-analysis. *J Am Soc Nephrol.* 1993;4:1300-1305.
- Kasiske BL, Chakkera HA, Louis TA, et al. A meta-analysis of immunosuppression withdrawal trials in renal transplantation. *J Am Soc Nephrol.* 2000;11:1910-1917.
- Ahsan N, Hricik D, Matas A, et al. Prednisone withdrawal in kidney transplant recipients on cyclosporine and mycophenolate mofetil - a prospective randomized study. *Transplantation.* 1999;68:1865-1874.
- Sinclair NR. Low-dose steroid therapy in cyclosporine-treated renal transplant recipients with well-functioning grafts; the Canadian Multicenter Transplant Study Group. *CMAJ.* 1992;147:645-657.
- Matas AJ, Ramcharan T, Parakevas S, et al. Rapid discontinuation of steroids in living donor kidney transplantation: a pilot study. *Am J Transplant.* 2001;1:278-83.
- Shapiro R, Jordan ML, Scantlebury VP, et al. Outcome after steroid withdrawal in renal transplant patients receiving tacrolimus-based immunosuppression. *Transplant Proc.* 1998;30:1375-1377.
- Grinyó JM, Gil-Vernet S, Seron D, et al. Steroid withdrawal in mycophenolate mofetil-treated renal allograft recipients. *Transplantation.* 1997;15:1688-1690.
- Matas AJ, Kandaswamy R, et al. Prednisone-free maintenance immunosuppression - a 5-year experience. *Am J Transplant.* 2005;5:2473-2478.
- Jaber JJ, Feustel PJ, Elbahoui O, Conti AD, Gallichio MH, Conti DJ. Early steroid withdrawal therapy in renal transplant recipients: a steroid-free sirolimus and CellCept-based calcineurin inhibitor-minimization protocol. *Clinical Transplantation.* 2007;21:101-109.
- Kirk AD, Hale DA, Mannon RB et al. Results from a human renal allograft tolerance trial evaluating the humanized CD52-specific monoclonal antibody alemtuzumab (CAMPATH-1H). *Transplantation.* 2003;76:120-129.
- Calne R, Moffatt SD, Friend PJ et al. Campath 1H allows low-dose cyclosporine monotherapy in 31 cadaveric renal allograft recipients. *Transplantation.* 1999; 68: 1613-1616.
- Knechtel SJ, Pirsch JD, Fecgner JJ, et al. Campath-1H induction plus rapamycin monotherapy for renal transplantation: Results of a pilot study. *Am J Transplant.* 2003;3: 722-730.
- Flechner SM, Friend PJ, Brockman J, et al. Alemtuzumab induction and sirolimus plus mycophenolate mofetil maintenance for CNI and steroid-free kidney transplant immunosuppression. *Am J Transplant.* 2005; 5:3009-3014.
- Kaufman DB, Leventhal JR, Axelrod D, et al. Alemtuzumab induction and prednisone-free maintenance immunotherapy in kidney transplantation: Comparison with basiliximab induction-long-term results. *Am J Transplant.* 2005; 5:2539-2548.
- Vathsala A, Ona ET, Tan SY, et al. Randomized trial of alemtuzumab for prevention of graft rejection and preservation of renal function after kidney transplantation. *Transplantation.* 2005; 80:765-774.
- Ciancio G, Burke GW, Gaynor JJ, et al. A randomized trial of three renal transplant induction antibodies: Early comparison of tacrolimus, mycophenolate mofetil, and steroid dosing, and newer immune-monitoring. *Transplantation.* 2005;80:457-465.
- Huang E, Cho YW, Hayashi R, Bunnapradist S. Alemtuzumab induction in deceased donor kidney transplantation. *Transplantation.* 2007;84(7):821-828.

RENAL TRANSPLANTATION FORUM REPORT™

Outcomes Using Reduced Calcineurin Inhibitors in Renal Transplantation

CME/CE Test Questions

- Which of the following adverse effects are potential considerations for reduction or elimination of calcineurin inhibitors?
 - Neurotoxicity
 - Nephrotoxicity
 - New-onset diabetes mellitus
 - Hypertension
 - All of the above
- In the study comparing high-dose tacrolimus with low-dose tacrolimus maintenance immunosuppression, what effect is observed on renal function?
 - Low-dose tacrolimus was associated with decreased glomerular filtration rate (GFR), but lower incidence of renal interstitial fibrosis
 - Low-dose tacrolimus was associated with decreased GFR, and higher incidence of renal interstitial fibrosis
 - Low-dose tacrolimus was associated with improved GFR, and lower incidence of renal interstitial fibrosis
 - Low-dose tacrolimus had a similar GFR to high-dose tacrolimus, but lower incidence of renal interstitial fibrosis
- What effect did reducing tacrolimus dosing have on the rate of polyoma virus nephropathy (PVAN)?
 - Lower doses of tacrolimus were associated with lower rates of PVAN
 - Lower doses of tacrolimus were associated with higher rates of PVAN
 - Dosing of tacrolimus had no effect on rates of PVAN
- In the study comparing efficacy and toxicities of four different immunosuppressive regimens, which regimen demonstrated better overall results regarding renal function, allograft survival, and acute rejection?
 - Standard-dose cyclosporine, mycophenolate mofetil, and corticosteroids
 - Daclizumab induction, mycophenolate mofetil, corticosteroids, and low-dose cyclosporine
 - Daclizumab induction, mycophenolate mofetil, corticosteroids, and low-dose tacrolimus
 - Daclizumab induction, mycophenolate mofetil, corticosteroids, and low-dose sirolimus
- In the study evaluating early steroid withdrawal, how did early steroid withdrawal impact survival compared with historical controls?
 - Early steroid withdrawal was associated with increased patient survival
 - Early steroid withdrawal was associated with decreased patient survival
 - There was no significant difference in patient survival between the early steroid withdrawal group and historical controls
- What effect did early steroid withdrawal have on weight gain?
 - Early steroid withdrawal was associated with increased weight gain
 - Early steroid withdrawal was associated with a reduction in weight gain
 - There was no significant difference in weight gain between the early steroid withdrawal group and the historical control group
- Compared to the control group, which of the following effects on cardiovascular risks were associated with early steroid withdrawal?
 - Lower incidence of post-transplant diabetes mellitus
 - Lower prevalence of hypertension
 - Lower prevalence of hyperlipidemia
 - All of the above
- In the study evaluating alemtuzumab efficacy, which of the following is most consistent with the study findings?
 - Alemtuzumab induction was associated with consistently lower rates of acute rejection throughout the study compared to other regimens
 - Alemtuzumab induction was associated with consistently higher rates of acute rejection throughout the study compared to other regimens
 - Alemtuzumab induction was associated with lower rates of acute rejection initially, however over time, the rates of acute rejection exceeded that of other regimens
 - None of the above

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Outcomes Using Reduced Calcineurin Inhibitors in Renal Transplantation

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The planning and execution of useful and educationally sound continuing education activities are guided in large part by input from participants. To assist us in evaluating the effectiveness of this activity and to make recommendations for future educational offerings, please take a few moments to complete this evaluation form. Your response will help ensure that future activities are informative and meet the educational needs of all participants. **Please note: CME/CE credit letters and long-term credit retention information will be issued only upon receipt of this completed evaluation form.** Thank you for your cooperation!

PROGRAM OBJECTIVES:

Having completed this activity, I am better able to:

	Strongly Agree			Strongly Disagree	
Discuss the benefits of early steroid withdrawal and replacement with sirolimus and mycophenolate mofetil to minimize calcineurin inhibitors in renal transplant recipients.	5	4	3	2	1
Compare the efficacy of alemtuzumab induction in conjunction with calcineurin inhibitor maintenance or calcineurin inhibitor-free therapy.	5	4	3	2	1
Examine low- and high-dose tacrolimus levels on rejection and adverse effects in renal transplant recipients.	5	4	3	2	1
Determine the impact of calcineurin inhibitor reduction on renal function and graft survival in renal transplant patients.	5	4	3	2	1

OVERALL EVALUATION:

	Strongly Agree			Strongly Disagree	
The information presented increased my awareness/understanding of the subject.	5	4	3	2	1
The information presented will influence how I practice.	5	4	3	2	1
The information presented will help me improve patient care.	5	4	3	2	1
The program was educationally sound and scientifically balanced.	5	4	3	2	1
Overall, the program met my expectations.	5	4	3	2	1
I would recommend this program to my colleagues.	5	4	3	2	1

The program was free of commercial bias or influence. Yes No (Please provide additional information below.)

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Complete the CE Registration and Answer Key. Please print or type your full name, address, and any other pertinent information in the space provided. Circle your answers to the Activity Self-assessment Test below. In order to be processed, information must be complete and legible.

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| 2. A B C D | 4. A B C D | 6. A B C | 8. A B C D |
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