Kidney transplantation, the best treatment of choice for most patients with end-stage renal disease, is associated with significant improvement in quality of life and decreases in mortality risk for most patients when compared with maintenance dialysis.1–3 The introduction of induction therapy following kidney transplantation, especially with the use of a lymphocyte-depleting agent in the mid-1970s and calcineurin inhibitor (CNI) therapy using cyclosporine in the early 1980s, decreased the rate of acute rejection and improved allograft survival during the first year after transplantation. Although 1-year graft survival rates are excellent, long-term graft survival over the past decade has been associated with only modest improvements. The survival of kidney-transplant recipients is significantly lower than that of age-matched controls in the general population.4,5 The relatively higher mortality in kidney-transplant recipients partially is due to comorbid medical illness; the duration of dialysis treatment pretransplant; and factors specifically related to the transplant process, including immunosuppression and other drug effects.6,7

Over the past 10 years, the overall rate of graft failure (return to dialysis, retransplant, death with a functioning graft) among transplant recipients has continued to trend downward (6.2/100 patient-years in 2011), although death with a functioning graft has plateaued (Figure 1).8 The main causes of death with a functioning allograft have been cardiovascular disease (31%) and infection (19%; Figure 2).8

In 2013, the United States Renal Data System noted that the percentage of kidney-transplant patients experiencing acute graft rejection had declined steadily over the past decade (Figure 3).8 Despite reduction of acute rejection with improvements in overall outcomes following renal transplantation, kidney-allograft loss remains common. It is essential to find out...
how to maximize outcomes and minimize renal-allograft failure.

This review is based on an Astellas-sponsored satellite symposium conducted during the 2014 World Transplant Congress in San Francisco, California. The panelists included Robert S. Gaston, MD, Professor of Medicine at the University of Alabama at Birmingham; Roy D. Bloom, MD, Medical Director of the Kidney and Pancreas Transplant Program at the Hospital of the University of Pennsylvania in Philadelphia; Arthur J. Matas, MD, Professor of Surgery at the University of Minnesota in Minneapolis; and Flavio Vincenti, MD, Professor of Medicine at the University of California at San Francisco.

RENA-LALLOGRAFT SURVIVAL

Despite significant improvements in 1-year kidney-allograft survival, chronic allograft loss after the first year remains common, and the rate has not improved over the past decade. Over the past 20 years, the major improvement in first-year renal-allograft survival has been due to reduced early attrition (Figure 4). A number of factors influence short-term graft survival, including delayed graft function, human leukocyte antigen (HLA) antibodies, type of donor kidney, and donor illness, among other factors.

Even though there has been a significant reduction in early attrition over the years, attrition rates have not improved dramatically, which influences long-term survival. The reasons for the lack of improvement in long-term survival remain unclear and are probably multifactorial. Possible factors are under immunosuppression (nonadherence, lack of efficacy), over immunosuppression (infection, malignancy), recurrent disease, poor organ quality, and patient death.

Causes of Allograft Loss

The causes of kidney allograft failure remain unclear. El-Zoghby et al10 investigated the causes of graft loss in 1,317 kidney allografts transplanted between January 1, 1996, and July 1, 2006. A total of 330 grafts (25.1%) were lost, 138 (10.5%) due to death with function, 39 (3.0%) to primary nonfunction, and 153 (11.6%) to graft failure censored for death. In all, more than half (53.6%) of the graft losses were associated with death with function and primary graft nonfunction. The causes of death after kidney transplantation in patients with functioning kidney allografts were related to cardiovascular factors (28.2%), infections (15.2%), malignancies (13.8%), and other (11.6%) or unknown phenomena (31.2%). The causes of 153 functioning graft losses not due to patient death included glomerular diseases (36.6%), fibrosis/atrophy (30.7%), medical/surgical condition (16.3%), acute graft rejection (11.8%), and unclassifiable factors (4.6%).

Risk Factors for Chronic Allograft Injury

The exact mechanisms responsible for chronic allograft injury leading to long-term graft loss are unclear. Both immunologic and nonimmunologic dependent factors may contribute to chronic allograft dysfunction. The immunologic factors comprise poor HLA matching, previous sensitization, history of acute graft rejection, inadequate immunosuppression, and patient nonadherence to their medication regimen. Nonimmunologic factors include comorbidities (ie, hypertension, diabetes, obesity), older donor or poor organ quality (eg, expanded-criteria donors), acute peritransplant injuries (eg, brain-death injury, ischemia, and/or reperfusion injury), chronic CNI toxicity (eg, nephrotoxicity, hypertension, hyperglycemia, dyslipidemia), and BK virus nephropathy.

To prevent acute rejection and allograft loss, all kidney-transplant recipients (except between identical twins) require immunosuppressive therapy. Immunosuppressants are used for induction (ie,
intense immunosuppression during the immediate peri- and post-transplant period to avert or delay the onset of acute rejection), maintenance immunosuppression, and reversal of established rejection.

**IMMUNOSUPPRESSION IN KIDNEY TRANSPLANTATION**

In the 1950s, when clinical renal transplantation began, the first attempts at immunosuppression relied on sublethal total-body irradiation. Administration of azathioprine was introduced in the early 1960s and was soon accompanied by prednisolone. The polyclonal antibody preparations antithymocyte globulin and antilymphocyte globulin became available in the mid-1970s. The introduction of cyclosporine in the early 1980s transformed clinical transplantation into preferred treatment, since it led to significant improvement in graft survival rates. Tacrolimus then was introduced as an alternative to cyclosporine; use of mycophenolate mofetil (MMF) soon followed. Daclizumab and basiliximab, humanized monoclonal antibodies directed toward the interleukin (IL)-2 receptor (CD25), were approved by the US Food and Drug Administration in 1997 and 1998, respectively, for use after kidney transplantation, based on their capacity to reduce the incidence of acute rejection episodes (Figure 5). The mammalian target of rapamycin (mTOR) inhibitor sirolimus became available for clinical immunosuppression in 1999, followed by the mTOR inhibitor everolimus in 2010 and the T-cell costimulation blocker belatacept in 2011.

**Induction Therapy**

A large number of randomized controlled trials and meta-analyses have demonstrated that induction therapy combining a biologic agent with conventional immunosuppressants is superior to conventional therapy alone in reducing kidney allograft rejection and allograft failure. Therefore, the 2009 Kidney Disease: Improving Global Outcomes (KDIGO) clinical practice guidelines recommended including a biologic agent as part of the initial immunosuppressive regimen for kidney-transplant recipients. The KDIGO guidelines specifically recommended that an IL-2 receptor antagonist, either daclizumab (no longer available) or basiliximab, be used as first-line therapy. However, the guidelines also suggested using a lymphocyte-depleting agent for kidney-transplant recipients who are at high immunologic risk or have risk factors for acute rejection.

**Maintenance Immunosuppression**

Maintenance of immunosuppression requires the continuous use of immunosuppressive medications to prevent acute
graft rejection. Specific medications have changed over the years, but maintenance immunosuppression represents the cornerstone of long-term antirejection therapy. Immunosuppressants currently being used in various combination immunosuppressant maintenance regimens (dual or triple therapy) include corticosteroids, azathioprine, MMF, mycophenolate sodium, cyclosporine, tacrolimus, sirolimus, everolimus, and belatacept. Matas et al\textsuperscript{15} reported that in the United States, approximately 85% of kidney-transplant recipients were discharged on tacrolimus and MMF, either with (58%) or without (42%) glucocorticoids.

Despite the ability of current immunosuppressive regimens to reduce the incidence of acute rejection, long-term toxicity related to the use of these drug combinations has become a major challenge. Chronic exposure to CNIs causes arteriolar hyalinosis leading to glomerulosclerosis, tubular atrophy, and interstitial fibrosis. The incidence of CNI nephrotoxicity increases with time after transplant.\textsuperscript{16} Therefore, there is a great interest in immunosuppressive regimens that permit reduction or elimination of CNIs while maintaining adequate immunosuppression. Several studies have investigated methods of minimizing, eliminating, or avoiding the use of CNIs.

\section*{CNI-Sparing Regimens}

Ekberg and others\textsuperscript{17} explored improvement of long-term renal function and promotion of allograft survival using CNI-sparing regimens. They randomized 536 patients receiving their first renal transplant into three groups: one was weaned from cyclosporine starting at month 4 post transplant and ending at month 6, a second received low-dose cyclosporine, and the third received standard-dose cyclosporine. The mean glomerular filtration rate (GFR) 12 months after transplantation (primary endpoint) was not statistically different in the cyclosporine-withdrawal and low-dose cyclosporine groups than it was in the standard-dose group. However, the incidence of biopsy-proven acute rejection (BPAR) was significantly higher in the cyclosporine-withdrawal group (38%) than in the low-dose (25.4%) or standard-dose (27.5%) cyclosporine groups (Figure 6).\textsuperscript{17}

CNI minimization in the SYMPHONY study\textsuperscript{18} showed that at 3 years after transplant, a regimen based on daclizumab induction, 2 g of MMF, low-dose tacrolimus, and a corticosteroid resulted in better renal function (as measured by GFR) and lower acute rejection and graft loss rates than did a regimen using a low dose of cyclosporine or sirolimus instead of tacrolimus and another involving no induction therapy and standard doses of cyclosporine.

Langer et al\textsuperscript{19} conducted a 12-month randomized, open-label, multicenter trial (ASSET) in de novo renal transplant recipients who received tacrolimus in combination with everolimus, basiliximab induction, and corticosteroids. In the first 3 months of the study, all patients received tacrolimus at daily doses sufficient to achieve a target trough level between 4 and 7 ng/mL. Thereafter, about half the patients (n = 109) continued at the same low trough target level, whereas the other half (n = 119) were given lower doses of tacrolimus to maintain a very low trough target level of 1.5–3 ng/mL. Everolimus trough target levels were 3–8 ng/mL throughout the study.

The authors found no statistically significant difference in mean estimated GFR between the low and very low tacrolimus trough level groups (57.1 vs 51.7 mL/min/1.73 m\textsuperscript{2}), possibly due to overlapping tacrolimus exposure levels.\textsuperscript{19} The incidence of BPAR during months 4–12 and the frequency of serious adverse events over the full course of the study also were comparable between the two groups.\textsuperscript{19} Thus, an everolimus-facilitated tacrolimus minimization regimen achieved good renal function, low BPAR and graft-loss rates, and an acceptable safety profile in renal-transplant recipients over 1 year, although statistically superior renal function was not achieved in the 1.5–3 ng/mL tacrolimus trough level group.

A number of randomized controlled trials have focused on CNI elimination with mTOR inhibitors using either sirolimus or everolimus. Schena and colleagues\textsuperscript{20} conducted CONVERT, a prospective, randomized, multicenter clinical trial that assessed the safety and efficacy of converting renal-allograft recipients from CNI maintenance therapy to sirolimus-based immunosuppression. In all, 830 renal-transplant recipients who were 6–120 months post transplant and receiving cyclosporine or tacrolimus were randomly assigned to continue their CNI regimen or converted to sirolimus.

At 2 years, sirolimus conversion among patients with a baseline GFR > 40 mL/min was associated with excellent patient and graft survival, no difference in BPAR, increased urinary protein excretion, and a lower incidence of malignancy when compared with CNI continuation. However, the enrollment of patients having a baseline GFR = 20–40 mL/min was halted prematurely because of a higher incidence of safety endpoints (eg, biopsy-confirmed acute rejection, graft loss, or death at 12 months) in the sirolimus conversion arm.

It should be noted that the use of mTOR inhibitors plus a CNI minimization regimen has nonrenal benefits, including a reduced incidence of cytomegalovirus infection, lower risk of BK viremia, and reduced intimal proliferation in heart-transplant recipients.

Vincenti and others\textsuperscript{21} conducted a ran-
Nonadherence is an important risk factor for renal graft loss over the long term. An accurate assessment of the frequency of medication nonadherence and its contribution to allograft loss is difficult because of the wide variability in study designs and results. Post-transplant nonadherence is common and has been reported in 5%–45% of renal-transplant patients. Schweizer et al conducted a retrospective and prospective study of medication noncompliance and follow-up care in 538 kidney-transplant recipients. The retrospective chart review of 260 patients transplanted between 1971 and 1984 revealed a medication nonadherence incidence of 18%, of which 91% of patients either lost their grafts or died. The prospective study also revealed a 15% nonadherence rate. Nonadherent behavior was usually not predictable and often had no identifiable reason.

Nonadherence rates increase dramatically > 6 months post transplantation. However, nonadherence is likely underestimated, because many studies are based on patient self-reporting. Gaston and colleagues evaluated the role of nonadherence in graft loss. The grafts of 1,005 kidney-transplant recipients survived for > 6 months between 1992 and 1995. However, 184 patients subsequently lost their grafts over 48 ± 11 months. The graft loss initially was attributed to chronic rejection. In all, 83 patients had chronic rejection, and 48 (26% of patients who lost their grafts) had not adhered to their maintenance immunosuppressive regimen. Medication nonadherence was deemed to be the primary cause of graft loss at their center.

While 1-year allograft survival has improved significantly, long-term survival of kidney transplants has improved little over the previous decade.

Impact of Medication Nonadherence

As observed at the beginning of this review, while 1-year allograft survival has improved significantly, long-term survival of kidney transplants has improved little over the previous decade. Late kidney-graft loss has been attributed to death with a functioning graft and chronic graft rejection, a phenomenon associated with chronic allograft nephropathy, interstitial fibrosis, and tubular atrophy. Medication nonadherence has been linked to graft dysfunction, chronic graft rejection, graft loss, and the presence of donor-specific antibodies (DSAs). Nonadherence has a significant impact on graft survival.

Sellarés et al prospectively studied biopsies of kidney-transplant patients who progressed to graft failure after a biopsy was performed to identify a cause. Failure was rare after T-cell–mediated graft rejection and acute kidney injury and was common after antibody-mediated rejection. Among patients who experienced loss of a kidney graft due to rejection, 17 of 36 (47%) were independently identified as being nonadherent by their physicians (Figure 7). In addition, nonadherence was more frequent among patients whose grafts progressed to failure than among those with viable grafts (32% vs 3%).
Thus, a common cause of graft loss is antibody-mediated rejection, which has been correlated with nonadherence in up to one half of cases.

Graft survival is associated with de novo donor-specific HLA antibody (dnDSA) formation. Nonadherent patients are more likely to have developed dnDSAs. In a prospective study, Wiebe et al followed 315 consecutive kidney transplants without pretransplant DSAs for a mean of 6.2 ± 2.9 years. In all, 47 of 315 patients (15%) developed dnDSAs. Independent predictors of dnDSA were HLA-DR1 mismatch and medication nonadherence. A total of 23 of 47 patients (49%) who developed dnDSAs were nonadherent with their immunosuppressive regimen. Median 10-year graft survival was lower for those with dnDSAs than for the group without dnDSAs (57% vs 96%; P < 0.001).

### Identifying Nonadherent Patients

Medication nonadherence is difficult to detect until it presents as graft rejection. Adherence can be determined by objective measures (eg, direct observation, serum or plasma drug levels, pill counts, refill records, and electronic monitoring) and by subjective measures (self-reporting). There is no perfect measure of adherence in clinical practice. More than one approach should be used to identify and measure nonadherence.

Dew et al performed a meta-analysis of 147 studies of kidney, heart, liver, pancreas, kidney-pancreas, lung, and heart-lung recipients that were published between 1981 and 2005. A limited number of studies investigated individual psychosocial risk factors with nonadherence outcomes. Few significant psychosocial variables (nonwhite ethnicity, poorer social support, and poorer perceived health) were significantly associated with greater immunosuppressant nonadherence. Other risk factors for nonadherence that were reported in subsequent studies included inability to make co-payments, patients’ beliefs about immunosuppressive medications, perceived lower life satisfaction and graft longevity, younger age, male gender, and receipt of a graft from a living donor.

### Approaches for Managing Nonadherence

There is no single cause for nonadherence, so it is difficult to have one effective intervention for its management. Successful intervention to improve medication adherence requires a team approach. Combinations of strategies that focus on patient education programs, convenience of the dosing regimen, social media, and electronic systems may be effective in the long term.

De Bleser and others systematically reviewed 12 trials designed to minimize post-transplant medication nonadherence and identified a number of weaknesses in the studies. Only five studies were randomized, controlled trials that found a statistically significant improvement in at least one medication-adherence outcome with the intervention. Therefore, no single intervention was better at increasing medication adherence than any other, but a combination of interventions provided by a team may be the best approach to improve long-term outcomes.

Another way to improve medication adherence is to simplify the dosing regimen. Several studies have shown once-daily dosing to be significantly associated with improved adherence compared with twice-daily or more frequent dosing. However, complex immunosuppressive regimens make interpretation of these results difficult, especially since immunosuppressants are generally taken once or twice daily.

Kuypers and colleagues performed a randomized, multicenter, controlled trial to evaluate differences in medication adherence between patients taking tacrolimus once daily and those taking the drug twice daily. An electronic monitor documented drug intake. A total of 219 patients were analyzed; 145 were dosed once daily, and 74 were dosed twice daily. At 6 months after randomization, 81.5% of the once-daily group and 71.9% of the twice-daily group had continued taking the drug (P = 0.082). A total of 88.2% of the once-daily group and 78.8% of the twice-daily group took the prescribed number of daily doses, a significant difference (P = 0.009). Implementation of once-daily dosing of tacrolimus was therefore associated with significantly higher adherence than twice-daily dosing.

Given the potentially devastating consequences of nonadherence to immunosuppressant therapy, clinicians should pay attention to medication adherence and discuss and monitor adherence with transplant recipients to improve long-term outcomes.

### LONG-TERM GRAFT SURVIVAL AND OUTCOMES

Long-term renal allograft survival in the United States has made small but mea-
survivable progress over the years. Identifying factors that may predict allograft loss is an important step toward prolonging kidney allograft survival.

Cosio et al. explored the association between histologic changes on 1-year surveillance biopsies and changes in graft function and survival. This study included 292 adult renal-allograft recipients; between 1998 and 2001, organs were transplanted from living or deceased donors, and patients were followed for an average of 46 ± 14 months. Fibrosis, inflammation, and transplant glomerulopathy were related to poorer survival, whereas mild fibrosis alone was not. Inflammation and glomerulopathy 1 year post transplant predicted loss of graft function and graft failure independent of function and other variables (Figure 8).

Gaston and others conducted an observational multicenter trial known as the Long-Term Deterioration of Kidney Allograft Function (DeKAF) study to identify modifiable variables that cause late allograft failure. They included 173 patients transplanted before October 1, 2005 (mean time after transplant, 7.3 ± 6.0 years), who had a baseline serum creatinine level of 1.4 ± 0.3 mg/dL before January 1, 2006. Patients underwent biopsy for new-onset graft dysfunction after that date (mean creatinine level at biopsy, 2.7 ± 1.6 mg/dL). The patients were analyzed by subgroup based on C4d staining and DSA status: group A was C4d−, DSA− (n = 71); group B was C4d−, DSA+ (n = 34); group C was C4d+, DSA− (n = 28); and group D was C4d+, DSA+ (n = 40). Among DSA+ recipients (groups B and D), those in group D had broader reactivity and a stronger DSA response than the C4d− patients in group B. After 2 years, groups C and D (C4d+) were at significantly greater risk for late graft failure and worse outcome than the C4d− patients in groups A and B (Figure 9). The immunologic insult (antibody-mediated injury) was substantially important in influencing long-term outcome when compared with the relative significance of nonimmunologic factors and progressive CNI toxicity.

Woodle and colleagues performed a 5-year prospective, randomized, double-blind, placebo-controlled, multicenter trial that compared early (7 days) corticosteroid cessation versus long-term, low-dose corticosteroid therapy. No differences in renal allograft survival and function at 5 years were observed between the two groups. Although early corticosteroid withdrawal was associated with less weight gain and improvement in serum triglyceride levels, it also increased the rate of BPAR (corticosteroid-sensitive).

**CONCLUSION**

Major advances achieved over the past decade have reduced the risk of acute graft rejection and increased short-term renal allograft survival. However, improving the long-term attrition rate in patient and graft survival remains challenging. Developing better immunosuppression strategies, introducing novel and less toxic agents or regimens, decreasing medication nonadherence, and addressing cardiovascular comorbidities such as hypertension and dyslipidemia should help to minimize graft failure and improve long-term outcomes.

A new paradigm in immunosuppression is required to improve long-term outcomes. New biologic agents should be designed to suppress both T and B cells, have less nephrotoxicity than current agents, not aggravate cardiovascular risk factors, not affect glucose metabolism, and improve adherence by requiring no more than once-daily dosing.

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