Improving Long-Term Outcomes After Kidney Transplantation

Jonathan C. Berger, MD, MHS
The University of Michigan Hospital and Health System, Ann Arbor, Michigan

Abstract Prolonged maintenance of a healthy kidney transplant involves keeping the patient and graft healthy while limiting the adverse effects of immunosuppressant therapy. At a state-of-the-art symposium held during the 2014 World Transplant Congress, experts in renal transplantation covered a number of topics related to improving patient and graft survival and promoting the quality of life of kidney transplant recipients receiving immunosuppressive therapy. Speakers also discussed the current status of immune monitoring of kidney-transplant patients and its potential to supplant HLA typing, cross-matching, and repeat biopsies in predicting the success or failure of immunosuppression.

In many ways, the fundamental challenge of managing a patient who has received a solid-organ transplant is sustaining the delicate balance between avoiding graft rejection and allograft damage and minimizing the morbidity associated with use of immunosuppressants. Long-term immunosuppressive therapy preserves the health of transplanted organs, but it also may lead to infectious, cardiovascular, and oncologic complications that can threaten the survival of both the graft and the patient. Kidney transplantation is the most well-established and widely disseminated segment of solid-organ transplantation. The success of this surgery often suggests that the same diagnostic and therapeutic approaches used in renal transplantation may be applied to transplantation of other organs as well. However, each type of organ transplant presents its own considerations and need for particular drug regimens.

One of the most significant challenges in transplantation is improving long-term outcomes. This expansive and relatively ambiguous task can become manageable if we consider more specific goals: (1) optimizing patient survival, (2) optimizing graft survival, and (3) thoughtfully managing immunosuppression to balance survival of the patient and of the graft. These critical subjects were discussed at a state-of-the-art symposium on improving long-term outcomes that was conducted during the 2014 World Transplant Congress in San Francisco, California.

DEALING WITH THREATS TO PATIENT SURVIVAL

Based on a presentation by Bertram Kasiske, MD, Professor of Medicine and Head of Transplant Nephrology, University of Minnesota Medical School, and Director of the Renal Division, Hennepin County Medical Center, Minneapolis, Minnesota.

Within the broader goal of improving long-term kidney-transplant outcomes, we may consider threats to patient survival specifically. We can start by thinking about four questions. First, what is the survival goal that we have for our transplant patients? Second, what are the specific causes of death that diminish their survival? Third, what are the risk factors that could predict these specific causes of death? Fourth, and finally, what remedies can be applied to these conditions?

Survival Goals

When devising a survival goal for our patients, we can start by comparing the survival of end-stage renal disease (ESRD) patients with that of the general population and thinking about the life-expectancy benefit that transplantation provides. The risk of death associated with ESRD is high. Further, when considering life-years lost, the effect of ESRD on mortality is most pronounced in younger patients. Therefore, younger transplant candidates have the highest potential for recovering these lost life-years.

Of course, older patients with ESRD also have life to be gained from transplantation; epidemiologic studies have demonstrated that patients with kidney transplants have better survival than do those who undergo peritoneal dialysis or hemodialysis, even though their survival is not equivalent to that of the general population.

Causes of Death

To improve survival after transplantation, we should consider the leading causes of death. Predictably, the number-one cause is a cardiovascular event, followed by infection and malignancy. These causes of death are similar among younger (age < 50 years) and older recipients.

Risk Factors

The most important risk factor, particularly for cardiovascular causes of death, is age. Obesity is another important risk factor. A body mass index > 30 kg/m² is associated with a 90% increased risk of cardiovascular death. Other risk factors for death related to cardiovascular disease...
are known vascular disease, diabetes, and cigarette smoking.

Preexisting comorbidities also associated with demise include cardiovascular disease, lung disease, pretransplant diabetes, and vascular disease. Importantly, increased time to transplant is an important risk factor; this likely relates to longer times on dialysis, as preemptive transplants are associated with lower cardiovascular mortality. Interestingly, the type and amount of immunosuppressant therapy used are not major risk factors for cardiovascular mortality post transplant.

Renal function also affects outcomes, as recipients with a higher glomerular filtration rate (GFR) have lower cardiovascular mortality than patients with low GFRs. Similarly, delayed graft function is a risk factor for cardiovascular death, as is use of deceased-donor renal transplants, as compared with grafting a kidney from a living donor. Increased cold ischemic time, however, is not a risk factor. Finally, human leukocyte antigen (HLA) mismatch (a five- to six-antigen mismatch as compared with a zero mismatch) is an independent risk factor for cardiovascular mortality. 4–7

Remedies

Once we have identified the risk factors, we should turn our attention to potential remedies. For this task, we should refer to the Kidney Disease: Improving Global Outcomes (KDIGO) guidelines. 7 Generated by an international work group and published in 2009, this evidence-based literature review supplies practitioners with recommendations for the care of typical kidney-transplant recipients. They were not intended to document standards of care.

Immunosuppressive therapy. Following guidelines for immunosuppression appears to be the key to maintaining kidney transplants. Since 2009, new immunosuppressants and new formulations of existing medications have been evaluated. For example, alemtuzumab and rabbit antithymocyte globulin (ATG) are often used as induction agents, even though their use in kidney transplantation as such has not been approved by the US Food and Drug Administration (FDA). Belatacept has been approved by the FDA for immunosuppression in patients receiving kidney transplants, but its benefits and risks compared with those of other, more established immunosuppressants have not yet been fully elucidated. The usefulness of rapamycin is similarly unclear, except that it likely affords a benefit over standard immunosuppressants in patients with skin cancer. Everolimus has a similar role to rapamycin. The benefit of enteric-coated mycophenolate mofetil (MMF) compared with that of standard MMF has not been established. Finally, the new formulation of once-daily tacrolimus may increase patient adherence to long-term immunosuppressive therapy.

Generally, the 2009 recommendations still hold. Induction immunosuppression should be instituted with an interleukin-2 receptor antagonist or anti–T-cell antibody, tacrolimus as the preferred calcineurin inhibitor (CNI), MMF as the preferred antiproliferative agent, and low-dose steroids (ie, prednisone) for the long term. 1

Management of diabetes and hypertension. What can we do for risk-factor modification beyond immunosuppressant management? Aggressive diabetes prevention and control, hypertension management, tobacco abstinence, obesity reduction, and the use of HMG-CoA (3-hydroxy-3-methyl-glutaryl-coenzyme A) reductase inhibitors (statins) and low-dose aspirin prophylaxis all have a role in reducing cardiovascular morbidity in kidney-transplant recipients. In terms of diabetes management, the KDIGO guidelines recommend that all kidney-transplant recipients be screened for new-onset diabetes with fasting plasma glucose levels, oral glucose tolerance testing, and/or target hemoglobin A1c level = 7.0%–7.5%. Aspirin prophylaxis may be beneficial in diabetic patients with no known cardiovascular disease, but the data are not strong. Thus, aspirin should be used according to patient preferences in this population. In terms of hypertension, the KDIGO guidelines advise a goal of 130/80 mm Hg; however, more recent data from the nontransplant population suggest that a more realistic goal with fewer adverse effects from treatment might be 140/90 mm Hg. 7

Control of dyslipidemia. The dyslipidemia guidelines in KDIGO are based on the National Kidney Foundation’s Kidney Disease Outcomes Quality Initiative guidelines and are not graded. The strategy from this group was to treat risk instead of simply targeting cholesterol goals. Recipients < 30 years of age may not need a statin if they are at low risk. In these patients, the risk of polypharmacy may outweigh the small risk reduction related to statin therapy. In most transplant recipients > 30 years of age, statin use is recommended, particularly in those who are known to have cardiovascular disease or diabetes mellitus or who meet the ALERT trial inclusion criteria (age 30–70 years, total cholesterol level of 155–270 mg/dL, predicted survival > 1 year). 8 This group encompasses the vast majority of kidney-transplant recipients and reflects the high burden of cardiovascular mortality in this patient population. 9

There is a paucity of high-quality data regarding tobacco cessation, obesity, and aspirin prophylaxis specifically in the transplant population. Despite this shortcoming, the workgroup recommendations regarding tobacco use and obesity are straightforward—at every visit, tobacco use and obesity should be assessed, and interventions should be offered at every opportunity. Low-dose aspirin prophylaxis is encouraged as a secondary prevention (level of evidence, 2B) in all patients with cardiovascular disease unless there are specific contraindications (eg, bleeding, allergy) to the daily use of aspirin.

Prevention of infection is another strategy to improve long-term survival of kidney-transplant recipients. Guidelines suggest cytomegalovirus (CMV) prophylaxis is advisable. Whereas KDIGO recommendations were initially for 3 months, recent data suggest extending prophylaxis to at least 6 months post transplant. Trimethoprim-sulfamethoxazole treatment is recommended for Pneumocystis pneumoniae prophylaxis for 3–6 months (level of evidence, 1B) as well as to prevent urinary tract infections, although fewer data are available to support the latter recommendation.

Vaccination guidelines encourage
the use of inactivated vaccines according to the Centers for Disease Control and Prevention’s Advisory Committee on Immunization Practices (ACIP) recommendations. Administration of live vaccines should be avoided in transplant recipients. Hepatitis B virus vaccination is highly encouraged prior to transplantation. All vaccinations, with the exception of influenza immunization, should be avoided during the first 6 months after transplantation. Patients at high risk for Epstein-Barr virus infections should be monitored with nucleic acid testing.

**Prevention of malignancy.** In terms of cancer prevention, routine standard screening in transplant recipients should be encouraged. Whenever possible, physicians should consider reducing immunosuppression in the context of active malignancy. One randomized, controlled study demonstrated that patients with skin cancer may benefit from a switch to sirolimus, which has been associated with a decrease in squamous cell cancer recurrence.

In summary, the pursuit of long-term patient survival post transplantation requires attention toward the comorbidities that affect those with ESRD. Cardiovascular, infectious, and neoplastic comorbidities should be anticipated, screened for, and treated in a systematic and evidence-based fashion.

**DEALING WITH THREATS TO GRAFT SURVIVAL**

Based on a presentation by Brian Nankivell, MBBS, MSc, PhD, MD, Department of Renal Medicine, University of Sydney and Westmead Hospital, Westmead, New South Wales, Sydney, Australia.

The 1980s was a seminal decade in the evolution of transplant management. Azathioprine, corticosteroids, and cyclosporine emerged as the foundation for long-term immunosuppression in renal transplantation. Other agents, including OKT3 and ATG, could be used to treat acute graft rejection. Furthermore, agents such as ganciclovir helped to minimize complications related to CMV infection. Over the next decade, tacrolimus and MMF refined the pharmacy of immunosuppression, further improving survival.

However, since those advancements became the standard of care, there has been little improvement in long-term outcomes following kidney transplantation. Data from cohorts of patients undergoing biopsy after renal transplantation suggest certain patterns in graft failure that might inform our strategies to preserve graft function. For example, BK virus infection tends to occur within the first year after transplantation and then is generally not a problem. T-cell–mediated rejection tends to occur relatively early after transplantation, but it has a persistent, low level of incidence long term. Acute antibody-mediated rejection (AMR) displays a bimodal distribution, with peaks both early and late after transplant.

This type of expression also is observed with chronic transplant glomerulopathy. Interstitial fibrosis and tubular atrophy (IF/TA) gradually builds with time.

**Chronic Allograft Nephropathy**

Chronic allograft nephropathy is a frequent finding on biopsy. This nonspecific diagnosis represents a pattern of tubular injury, not a specific etiology. There are multiple causes for this finding, including graft rejection, ischemia/reperfusion injury, or infection with the BK virus. These insults can affect the interstitium of the kidney and damage the tubules.

If fibrosis and atrophy are bad, the combination of inflammation and IF/TA (i-IF/TA) is worse. This also may be the result of acute rejection in the context of chronic glomerulopathy. Importantly, the prognosis of i-IF/TA is much worse than IF/TA alone and ultimately leads to more fibrosis and graft loss.

**CNI Toxicity**

The introduction of cyclosporine and especially tacrolimus has led to progress in decreasing the development of i-IF/TA, likely because there is less immune-mediated injury with tacrolimus than with cyclosporine. However, CNI toxicity can contribute to arteriolar hyalinosis, which ultimately contributes to ischemic glomerulosclerosis. Over time (generally 5–15 years post transplant), this phenomenon increases, even with the use of low-dose tacrolimus regimens.

Notably, CNI toxicity without graft rejection has a better prognosis than it does if rejection is present; however, when it can be identified, the problem of CNI toxicity has effective solutions.

Strategies for avoiding CNI toxicity include minimizing exposure to CNIs by reducing their dosage or eliminating these drugs entirely by increasing the use of corticosteroids and antimetabolite therapy concomitantly with low-dose CNI therapy. Finally, CNIs may be replaced with alternative therapies, such as sirolimus or everolimus.

All of these strategies to treat CNI toxicity can be effective, but one must be cognizant of the risk of graft rejection. In patients who are not affected by rejection, CNI minimization or elimination does not increase the risk of rejection when corticosteroids and antimetabolites are used thoughtfully. In those at high risk of graft rejection, the use of sirolimus or everolimus with CNI minimization or elimination may be more prudent.

**Late Rejection**

In terms of late threats to the renal graft, late rejection is an important problem that almost always is related to underimmunosuppression and often is associated with medication nonadherence. Late rejection is often acute and is both antibody and cellular mediated. It is associated with de novo donor-specific antibody (DSA) and can initiate a chronic response resulting in nephron loss. Histologically, this process manifests as a T-cell interstitial infiltrate and corresponding tubulitis. The presence of complement results in T-cell and macrophage recruitment, initiating chronic transplant glomerulopathy. In these cases, the presence of de novo DSAs is a negative prognostic indicator. However, not all DSAs are bad. The presence of DSA in the absence of evidence of graft rejection on protocol biopsies is not associated with worse outcomes. Stable graft function in the presence of DSA may indicate subclinical rejection, which may contribute to chronic glomerulopathy and indicate the need for biopsy.

Risk factors for late rejection are similar to those of early rejection. Afri-
can-American race, class 2 HLA antigen mismatch (particularly DQ), and medication nonadherence are all associated with development of de novo DSAs and late rejection. Under immunosuppression may be related to iatrogenesis associated with physicians withholding immunosuppression (for sepsis, BK virus, malignancy, or side effects) or patient nonadherence due to the development of side effects such as tremors, hirsutism, mood swings, or lifestyle changes. In typical patients maintained on triple immunosuppressive therapy, eliminating any one agent will increase the risk of graft rejection. Unfortunately, medication adherence rates have been as low as 23%–50% in some studies. Effective strategies to prevent nonadherence include educational programs, often with a specialized transplant pharmacist, and efforts to minimize the complexity of immunosuppressive regimens. For example, once-daily dosing of tacrolimus may help to resolve issues of nonadherence.

Adverse Reactions

Side effects of immunosuppression contribute to patient nonadherence. Pathologically, late rejection is typified by inflammation with broad immune activation (cellular, humoral, and innate), tissue destruction with architectural distortion, infiltration with a variety of leukocytes (T cells, B cells, eosinophils, polymorphonuclear lymphocytes, etc), and often DSA, exhibited by C4d positivity. Unfortunately, graft survival after late AMR is worse than after early AMR. This poor prognosis is related to the relatively low efficacy of current therapies for AMR (ie, bortezomib, eculizumab, rituximab, intravenous immunoglobulin) combined with the presence of chronic low-level graft injury and fibrosis. Data to support the use of these therapies are relatively weak, and use of these medications to combat AMR is still off-label.

Thus, the main late threat to graft failure is the alloimmune response. Donor quality and CNI toxicity also are important. Late rejection is usually mixed, and chronic subclinical rejection slowly leads to nephron loss. Preventive strategies are important to enhance medication adherence and minimize graft injury. These strategies include education as well as aggressive management of hypertension and diabetes. Biopsy should be used aggressively to identify a specific diagnosis. Where multiple processes are present, the dominant phenotype should be treated. Unfortunately, the existing therapies for late rejection are suboptimal, and further research in this field is sorely needed.

### IMMUNE MONITORING: A RATIONAL APPROACH TO MANAGEMENT OF IMMUNOSUPPRESSION

**Based on a presentation by Peter Heeger, MD, Professor of Medicine, Director of Transplant Research, and member of the Immunology Institute and Recanati Miller Transplant Institute, Icahn School of Medicine, Mount Sinai Hospital, New York, New York.**

Can immune monitoring be used to guide immunosuppression management? There has been significant progress in the field, but reliable, commercially available assays that can be used by clinicians to monitor a transplant recipient’s immune status are not yet available. As has already been discussed, long-term results are suboptimal. Many patients might tolerate less immunosuppression and do well with less medication. Other patients experience graft failure despite tight adherence to protocols.

These consequences suggest that there is a strong need in transplantation for biomarkers that can help move the field away from protocol-driven therapies and toward individualized immunosuppression. Our current approach to immune monitoring involves HLA typing, crossmatching, and biopsies. We use induction therapies and multidrug regimens, often starting at high doses and tapering over time. In these systems, clinical risk assessment (ie, age, previous transplant, DSA/panel-reactive antibody levels, living vs deceased donor, race) is used to guide immunosuppression. Unfortunately, these strategies are insufficient. Attempting tacrolimus withdrawal in so-called low-risk recipients often results in development of DSAs or graft rejection (unpublished data). Ideally, serially monitored post-transplant biomarkers could be used to better identify patients who could tolerate immunosuppression minimization than can clinical risk assessment. Acute graft rejection remains an important problem, even though its rates have declined. We have already seen poor long-term outcomes among those who experience acute rejection. Early, noninvasive detection of graft rejection (particularly treatable cellular rejection) may improve outcomes.

**Antidonor Memory T Cells**

One strategy being pursued involves an understanding of antidonor memory T cells. If antidonor T cells are present before transplant, cellular rejection rates are higher, and the GFR is lower at 12 months post transplant. These data have been validated in multiple studies. Are there any strategies to treat or eliminate antidonor memory T cells? Studies suggest that the absolute number of these cells may be depleted by ATG. However, the clinical effect of this depletion in terms of rejection and graft survival has not been described rigorously. Some data suggest that patients who receive ATG have a lower antidonor T-cell response during the first 6 months after transplant.

An effort to understand this phenomenon and to identify some noninvasive monitoring tests was undertaken in the CTOT-01 trial. In this nonrandomized, multi-institutional, observational study of 280 kidney recipients, the markers studied included pretransplant antidonor interferon γ memory T cells by the enzyme-linked immunospot (ELISpot) assay and several urinary biomarkers. ATG was used at the discretion of the transplant center. Patients who received ATG demonstrated lower post-transplant antidonor interferon γ memory T cells after the first 6 months. Furthermore, among those individuals with a positive pretransplant interferon γ ELISpot assay result, those who did not receive ATG had a lower GFR in 6 months than did those who had received it. Among all patients who received ATG, being ELISpot-positive was not associated with having a lower GFR. This was an observational study, so inferences from it are limited.
however, the results suggest that ATG may improve outcomes by depleting memory T-cell populations. 32

Some studies also have suggested that targeted therapies toward CD2, which is expressed on some memory T cells, may deplete memory T cells and decrease the incidence of graft rejection. Thus, memory T-cell analysis may be a promising biomarker to guide therapy. 29,30

Urinary Markers

There are also urinary markers to identify acute cellular rejection. Urinary cell messenger RNA profiling has detected a change in gene profiles up to a month before cellular rejection was clinically identified. 31 Urinary gene profiling also may be able to differentiate between cellular-mediated rejection and AMR. 32 In addition, urinary chemokines can differentiate patients with acute rejection. Some protein values (in particular, chemokine [C-X-C motif] ligand 9 [CXCL9], CXCL10) reliably increase up to several months before rejection occurs. 33 If the CXCL10 reliably increase up to several months before rejection occurs. 33

In addition, urinary chemokines can differentiate patients with acute rejection. Some protein values (in particular, chemokine [C-X-C motif] ligand 9 [CXCL9], CXCL10) reliably increase up to several months before rejection occurs. 33 If the ELISpot and urinary biomarker strategies are combined, we may acquire even more useful information. Patients with negative pretransplant ELISpot assay results and negative urinary CXCL9 levels at 6 months had a significantly higher GFR than did those who had either a positive ELISpot test result or CXCL9 in their urine. Peripheral blood monitoring also can be used. Recently presented data (the GoCAR study, unpublished) suggested that subclinical rejection could be detected at 3 months post transplant with a nine-gene set panel.

Clearly, we have useful data. The next challenge will be to standardize and commercialize assays to introduce these biomarkers into clinical practice. We need data from clinical research studies to determine whether biomarker-based assays truly can identify transplant patients at risk for rejection early and function as a noninvasive substitute for biopsies. Partnerships between academic institutions, government agencies, and industry will be needed to develop and disseminate this technology. This strategy holds promise to improve patient care in a cost-effective manner.

REFERENCES