Chronic kidney disease (CKD) develops frequently after nonrenal solid-organ transplantation and is associated with substantially increased morbidity and mortality. Multiple factors contribute to CKD risk in this patient group, including level of pretransplantation renal function, recipient demographics and comorbidity, acute kidney injury (AKI) during the perioperative period, and longer term calcineurin inhibitor (CNI) exposure. Strategies to minimize nephrotoxic insults and retard progressive renal injury are discussed, as are issues that are pertinent to dialysis and transplantation. Finally, future approaches to prevent and treat CKD without compromising function of the transplanted organ are addressed.

PREVALENCE OF CKD AFTER NONRENAL ORGAN TRANSPLANTATION

Historically, CKD prevalence rates in nonrenal organ recipients have ranged from 10 to 90%. This wide range is partly explained by a lack of consensus criteria as to what constitutes CKD in these populations and by shortcomings of estimating equations that depend on serum creatinine. Transplant candidates and recipients often have lower muscle mass and less creatinine generation than the populations in which these equations were developed, limiting the accuracy of the equations. This problem is exemplified in a large cohort study in which iothalamate GFR measurements were performed in 1447 liver transplant candidates before and sequentially after transplantation. Comparison of this "gold standard" measurement was made to GFR estimates that were based on serum creatinine, using the Modification of Diet in Renal Disease (MDRD) Study, Cockcroft-Gault, and Nankivell formulas. The mean pretransplantation, serum creatinine was 1.15 mg/dl, and the mean iothalamate GFR was 90.7 ml/min. Of all formulas, the six-variable MDRD fared best, although it lacked precision and underestimated renal function in patients beyond the first posttransplantation year. Recent studies suggest that the formulas are similarly limited in estimating kidney function in lung and heart recipients as well.

The largest and most comprehensive study of CKD prevalence after solid-organ transplantation used a definition of GFR of \(<30\) ml/min per 1.73 m² body surface area, calculated with the four-variable MDRD equation. Applying this definition to a data set from the Scientific Registry of Transplant Recipients (SRTR), Ojo et al. reported a CKD prevalence at 5 yr after transplantation of 21.3% among intestine recipients, 18.1% among liver recipients, 15.8% among...
lung recipients, 10.9% among heart recipients, and 6.9% among heart-lung recipients. More expansive definitions of CKD, such as GFR < 60 ml/min or presence of albuminuria, would have led to higher prevalence estimates.

More recently, using the Kidney Disease Outcomes Quality Initiative (KDOQI) classification system, O’Riordan et al. \(^8\) examined the risk for CKD by stage among 230 liver recipients who were followed for a mean of approximately 6 yr. Overall point prevalences of CKD among survivors at 10 yr was 2.26% with stage 5, 6.11% with stage 4, 56.77% with stage 3, 23.71% with stage 2, and the rest with minimal or no renal function deficit. In data from the SRTR, among nonrenal organ recipients who survived the first 3 posttransplantation months, 4% required maintenance dialysis within a median of 3 yr after transplantation.\(^1\) In the future, in concert with improving survival, it is probable that ESRD rates will proportionately increase in this population.

**RISK FACTORS FOR CKD AFTER TRANSPLANTATION**

**Renal Function before Transplantation**

The level of kidney function before organ transplantation is an important risk factor for posttransplantation CKD. Reliance on serum creatinine alone typically leads to an overestimation of renal function in patients before transplantation, particularly in those with poor nutritional status, low muscle mass, weight loss, and edema.\(^5,14\) Kidney function in patients who are awaiting nonrenal transplantation is frequently compromised by poor effective circulating volume (e.g., low cardiac output in advanced heart failure, hepatorenal syndrome in liver candidates) that is not always reversible after successful placement of a functioning organ (Figure 1).\(^2,15\) For instance, in a retrospective cohort study of heart recipients, more than one third of patients had stage 3 or worse CKD before transplantation. Preoperative renal disease was a strong risk factor for perioperative AKI requiring dialysis.\(^16\)

The utility of pretransplantation kidney biopsy for assessing cause and severity of kidney injury is not established. In many cases, impaired kidney function is hemodynamically mediated, and biopsy may have limited diagnostic value. Even when the cause is unclear, consideration of renal biopsy is often tempered by a heightened procedural risk as a result of coagulopathy, hemodynamic instability, or respiratory compromise.\(^17\)

**Demographic and Comorbid Factors**

Baseline recipient demographics and comorbidities also relate to CKD risk after organ transplantation. Several studies have shown that both advancing age and female gender confer greater risk for development of CKD, likely as a result of overestimation of pretransplantation renal function in the context of lower muscle mass.\(^1,18,19\)

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**Figure 1.** Relationship between acute kidney injury (AKI) and chronic kidney disease (CKD) in the nontransplantation population (A) and after nonrenal solid-organ transplantation (B). Many factors contribute to CKD risk in nonrenal organ recipients, including unrecognized preexisting CKD with superimposed AKI, pretransplantation insults leading to AKI, and exposures peri- and postoperatively. Whereas near complete recovery from AKI is the rule for patients without end-stage organ failure (A), the multitude of risk factors in nonrenal organ recipients leads to CKD in the majority of patients after transplantation (B). CNIs, calcineurin inhibitors; CO, cardiac output; DM, diabetes; HCV, hepatitis C virus; HRS, hepatorenal syndrome; HTN, hypertension; txp, transplant.
Diabetes and hypertension, common comorbidities among liver and heart transplant candidates, increase risk for renal disease. Preexisting kidney disease may be masked in these cases if serum creatinine is used as the renal function marker.\textsuperscript{1,5,15,19} Hepatitis C virus (HCV) infection has also been recognized as an important risk factor for CKD in liver and heart transplant patients. HCV-related cirrhosis is the major indication for liver transplantation, with 41% of liver recipients in 2004 infected with this virus.\textsuperscript{1,20} The CKD risk in liver recipients with HCV infection is primarily due to glomerulonephritis (GN). McGuire et al.\textsuperscript{21} recently described 30 HCV-infected patients who had cirrhosis and underwent kidney biopsy at the time of liver transplantation. The median serum creatinine level was 1.4 mg/dl; 13 patients had normal serum creatinine and urinalysis. Renal biopsies demonstrated immune complex GN in >80% of patients, most commonly membranoproliferative GN, followed by IgA nephropathy and mesangial GN. The clinical significance of such histologic abnormalities in liver and other nonrenal organ recipients with normal renal laboratory parameters, however, is unknown. The importance of recognizing pretransplantation renal function deficits is underscored by the observation that CKD before transplantation portends poor posttransplant survival.\textsuperscript{10,15,22,23}

**Perioperative Renal Insults**

AKI during the peritransplantation period creates additional risk for posttransplantation CKD (Figure 1). Mechanisms during and after surgery that may precipitate AKI include hypotension and hypoperfusion, administration of nephrotoxic agents such as radiocontrast, sepsis, and aggressive diuresis. With heart and/or lung transplantation, AKI may also be triggered by aortic cross-clamp, ventricular dysfunction with poor cardiac output, or atheroembolism.\textsuperscript{2} Acute dialytic requirement bodes particularly poorly for both patient and kidney outcomes.\textsuperscript{24,25} Dysfunction of the transplanted organ may also be associated with renal decompensation. Rocha et al.\textsuperscript{22} published a retrospective study of lung recipients, 56% of whom had AKI defined as a doubling of serum creatinine within 2 wk postoperatively, and 7.7% required dialysis. Requirement for mechanical ventilation for >1 d was associated with a greater than six-fold higher risk for AKI. Impaired kidney function in the setting of effective volume contraction has been observed early after both liver and heart transplantation.\textsuperscript{5,17,26}

**Polyomavirus BK Infection**

Although polyomavirus nephropathy (PVN) is an increasingly important cause of renal injury in kidney recipients, the virus’s role in contributing to CKD in nonrenal organ transplant patients is poorly defined.\textsuperscript{27} Prevalence rates of BK viruria ranging from 7 to 32% have been reported in nonrenal recipients, but viremia is observed less frequently.\textsuperscript{28–30} Cases of biopsy-proven PVN have been described in heart transplant patients.\textsuperscript{31,32} Larger scale observational studies incorporating serial BK viremia screening are required to determine whether PVN is an unrecognized and clinically important risk factor for CKD among nonrenal organ recipients.

**NEPHROTOXICITY CAUSED BY CNIs**

CNIs cause renal vasoconstriction that predisposes patients to AKI and chronic kidney injury, particularly when other insults are present. CNI nephrotoxicity has been studied most extensively with cyclosporin A (CsA), although the general mechanisms likely apply to tacrolimus as well. In organ recipients during the CsA era, the steepest decline in kidney function was shown to occur within the first 6 mo after transplantation. CNI-associated chronic nephrotoxicity increases with duration of exposure and has limited potential for reversibility.

**Acute Effects on the Kidney**

Acutely, CNIs induce reversible vasoconstriction of afferent and efferent glomerular arterioles that is maximal several hours after peak serum concentrations and declines as serum concentration gradually reach the trough.\textsuperscript{33} The net effects of these acute changes are reversible, concentration-related reductions in GFR and increases in renovascular resistance. Vasconstriction seems to be mediated by nitric oxide inhibition, by increased angiotensin II and thromboxane levels, and by augmented endothelin activity.\textsuperscript{34–36} These abnormal responses may be potentiated in the presence of other inhibitors of autoregulation, such as renin-angiotensin-aldosterone-system (RAAS)-blocking agents or nonsteroidal anti-inflammatory drugs.

**Chronic Nephrotoxicity**

Chronic CNI nephropathy has been extensively studied but remains incompletely understood. The typical clinical picture of chronic CNI nephropathy is characterized by a lack of symptoms, a bland urine sediment, and gradual decline in renal function. Albuminuria is common, although nephrotic-range proteinuria is a rare finding that should precipitate suspicion for other causes of renal disease.\textsuperscript{35} Renal biopsy studies among nonrenal organ recipients with CKD have shown that CNI-related injury is a common finding.\textsuperscript{7,14,37} Histopathologic findings include interstitial fibrosis with a “striped” appearance, nodular arteriolar hyalinosis, and, later, tubular atrophy with glomerulosclerosis and arteriosclerosis.\textsuperscript{14,38} Renal hemodynamic studies in CsA-treated patients have revealed decreased GFR in association with reduced blood flow, elevated mean arterial pressure, increasing renal vascular resistance, and albumin excretion.\textsuperscript{7} Over time, these perturbations result in progressive arteriolopathy and glomerular ischemic collapse. Hyperfiltration injury occurs in remaining nephrons, sometimes leading to ESRD.\textsuperscript{7}

Direct and indirect mechanisms of chronic CNI-mediated renal injury have been proposed. Direct mechanisms include that CNIs may increase oxidative stress, leading to systemic inflammation with deleterious effects on endothelial function.\textsuperscript{39,40} CsA in particular may up-
Conclusions of CKD After Solid-Organ Transplantation

The devastating consequences of CKD among solid-organ recipients resemble the health problems that are endemic in the nontransplantation population with kidney disease. These health concerns include increased rates of cardiovascular disease, hypertension, anemia, and bone disease.

Nonrenal solid-organ transplant recipients have a shorter lifespan compared with the general population, but their average survival is further compromised when CKD develops. Data from the 2005 Organ Procurement and Transplantation Network (OPTN)/SRTR Annual Report indicated that the baseline 5-yr survival ranged from 90.6% for pancreas-alone transplant recipients to 40.2% for heart-lung transplant patients. Ojo et al. reported that the relative risk for death after development of CKD in nonrenal organ recipients was 4.55. This elevated mortality risk was present even before dependence on renal replacement therapy, although it was highest for recipients who were on dialysis.

Hypertension is a commonly observed posttransplantation complication, occurring in >70% of lung, heart, and liver recipients. CNIs are important contributors to posttransplantation hypertension, often characterized by a low renin and aldosterone state. Ishani et al. demonstrated that diastolic BP elevation is an independent predictor of progressive kidney disease after lung or heart-lung transplantation. This observation is consistent with those in nontransplantation patients.

Anemia may also complicate the treatment of solid-organ recipients with CKD. Besides erythropoietin deficiency, additional factors that contribute to anemia include immunotherapies such as azathioprine, mycophenolate acid, and sirolimus, as well as patient comorbidities. Anemia has a negative impact on quality of life and may be of particular concern in patients with cardiovascular or pulmonary disease.

The prevalence of CKD-related bone disease in solid-organ transplant patients has not been well studied. In addition to derangements of their mineral metabolism, these patients may develop bone disease related to corticosteroids.

Organ-Specific Considerations Regarding Kidney Disease After Transplantation

Liver Transplantation

Before liver transplantation, abnormal renal function is frequent. Manifestations range from limited elevations in serum creatinine to frank hepatorenal syndrome that requires dialysis. Early postoperative kidney injury also occurs commonly, often in the setting of effec-
Table 1. Organ-specific considerations in CKD after nonrenal solid-organ transplantation

<table>
<thead>
<tr>
<th>Organ</th>
<th>Considerations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liver</td>
<td>perioperative AKI frequently as a result of HRS and/or volume depletion</td>
</tr>
<tr>
<td></td>
<td>stage 4 or 5 CKD present in 20% of patients by 5 yr after transplantation</td>
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<tr>
<td></td>
<td>high prevalence of HCV, subclinical glomerulonephritis common</td>
</tr>
<tr>
<td></td>
<td>increased risk for new-onset diabetes</td>
</tr>
<tr>
<td></td>
<td>lower maintenance dosages of CNI often adequate</td>
</tr>
<tr>
<td>Heart and lung</td>
<td>hemodynamic kidney insults common peroperatively</td>
</tr>
<tr>
<td></td>
<td>higher CNI dosing because of increased risk for rejection</td>
</tr>
<tr>
<td></td>
<td>chronic effective volume contraction is common and may lead to chronic ischemic renal injury</td>
</tr>
<tr>
<td></td>
<td>hypovolemia/overdiuresis</td>
</tr>
<tr>
<td></td>
<td>low cardiac output state</td>
</tr>
</tbody>
</table>

aAKI, acute kidney injury; CKD, chronic kidney disease; CNI, calcineurin inhibitors; HCV, hepatitis C virus; HRS, hepatorenal syndrome.

Table 2. Recommendations to protect residual renal function in nonrenal solid-organ transplant recipients with CKD

<table>
<thead>
<tr>
<th>Pre- and Peritransplantation</th>
<th>After Transplantation</th>
</tr>
</thead>
<tbody>
<tr>
<td>High suspicion for pretransplantation CKD</td>
<td>CNI-sparing regimens</td>
</tr>
<tr>
<td>Avoid hypotension</td>
<td>Tacrolimus over CsA</td>
</tr>
<tr>
<td>Minimize nephrotoxic agents</td>
<td>Maintain euvoemia</td>
</tr>
<tr>
<td>Optimize renal perfusion</td>
<td>Optimize renal perfusion</td>
</tr>
<tr>
<td></td>
<td>Aggressively treat hypertension per JNC VII</td>
</tr>
<tr>
<td></td>
<td>ACE inhibitors and/or ARB</td>
</tr>
<tr>
<td></td>
<td>Manage hyperglycemia and dyslipidemia per ADA and KDOQI guidelines</td>
</tr>
<tr>
<td></td>
<td>Vigilance for adverse drug interactions</td>
</tr>
</tbody>
</table>

aACE, angiotensin-converting enzyme; ADA, American Diabetes Association; ARB, angiotensin receptor blocker; CsA, cyclosporin A; JNC VII, Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure; KDOQI, Kidney Disease Outcomes Quality Initiative.
Principles of KDOQI
Our approach to treating organ recipients with CKD is guided by the same principles used in general CKD populations as outlined by KDOQI (Table 2).73 For the most part, the principles of CKD management described in KDOQI have not been tested and validated in nonrenal organ recipients. Nonetheless, we believe that the mechanisms and consequences of kidney injury are similar to those in general CKD populations. Therefore, we advocate treatment of BP according to the Joint National Committee VII guidelines; management of anemia, bone disease, and dyslipidemia according to KDOQI; and glycemic regulation using American Diabetes Association criteria.74

RAAS Blockade
Studies of CKD and proteinuria in nontransplantation patients demonstrate that ACE inhibitors and angiotensin receptor blockers exert renoprotective effects independent of BP control.75,76 There is a paucity of literature on the renal benefits of RAAS blockade in nonrenal solid-organ recipients, although one study demonstrated that these agents can be safely used in heart transplant patients for controlling hypertension.77 In retrospective studies of kidney recipients, RAAS blockade slowed progression of chronic allograft nephropathy and reduced circulating levels of TGF-β.78,79 Because TGF-β mediates CNI-related fibrosis, RAAS blockade may retard renal injury by disrupting this mechanism. In support of this notion, kidney biopsies from heart and lung transplant patients with CsA nephropathy demonstrated less TGF-β expression among patients who received ACE inhibitors than in those who did not.42 Recent experimental data also suggest a direct role of RAAS activation in promoting CKD and kidney fibrogenesis in nonrenal solid-organ recipients.45,46 Besides the renoprotective advantages of RAAS blockade, two other potential benefits in select nonrenal organ transplant settings are (1) induction of uricosuria and reduction of uricemia in heart recipients who are treated with losartan80 and (2) decreased hepatic fibrosis in liver recipients with recurrent HCV infection.81

CNI-Sparing Therapy with Mycophenolate Mofetil or Sirolimus
The presence of CKD in nonrenal organ recipients creates an opportunity for the nephrologist to initiate discussion about lowering CNI exposure to the minimum level for effective immunosuppression. We strongly recommend that this decision be made together with the patient’s transplant team, because the potential benefit of protecting kidney function must be weighed against risk to the transplanted organ. Lowering cumulative CNI exposure has beneficial effects on renal function and may lead to improvements in BP, glucose regulation, volume status, and dyslipidemia.55

CNI-sparing therapy can take the form of either minimization or withdrawal. Sparing therapy is usually attempted while adding or increasing mycophenolate mofetil (MMF) or sirolimus. Studies in heart, lung, and liver recipients have shown that serum creatinine and BP can improve when CNI exposure is reduced in concert with MMF addition.82–84 Similarly, in liver recipients in whom immunosuppression requirements are less stringent, emerging data suggest that elimination of CNIs and replacement by MMF may also achieve these goals.85 In contrast, there is growing recognition that sirolimus is not devoid of nephrotoxicity, as originally hoped. Sirolimus potentiates nephrotoxicity of CNIs, especially CsA.55,86–88 In the absence of convincing evidence of benefit, we advocate caution if the addition of sirolimus to a minimized CNI regimen is done for the purpose of attenuating renal injury. In addition, besides an association with thrombotic microangiopathy, reports have recently described increasing proteinuria in sirolimus-treated kidney and islet transplant patients.89,90 As opposed to a CNI-minimization approach, several retrospective studies in nonrenal organ recipients have investigated conversion to sirolimus as part of a CNI-withdrawal strategy to protect renal function. Results have generally been conflicting with both CsA91–94 and tacrolimus.95 Ongoing, prospective clinical trials should establish whether conversion to sirolimus preserves kidney function and whether level of kidney function at the time of conversion determines the utility of this strategy.

Dialysis and Sequential Kidney Transplantation
In keeping with KDOQI guidelines, timely preparation forrenal replacement therapy is essential for nonrenal organ transplant patients with declining kidney function. In light of an SRTR analysis demonstrating superior long-term outcomes compared with dialysis among previous nonrenal organ recipients, sequential kidney transplantation should be considered the ESRD treatment of choice for appropriate candidates.1 Early referral to the transplant center, prompt placement on the waiting listing, and consideration of live donors will likely further enhance outcomes for such patients. Given the high mortality observed in patients who are awaiting kidney transplantation, the use of lesser quality deceased donor organs, such as extended-criteria or cardiac death donors, may be a reasonable consideration to shorten waiting times, although no published data exist on this subject.

Dialysis has a high mortality rate and exerts substantial burdens on patient quality of life. Most organ recipients who need renal replacement therapy undergo hemodialysis (HD), although small series of transplant recipients undergoing peritoneal dialysis (PD) have been reported. Jayasena et al.96 performed a study of 17 heart and heart-lung transplant recipients who underwent PD. An increased frequency of peritonitis was observed in these patients compared with a control group who were immunosuppressed because of either autoimmune disease or recent transplant failure. Another small observational study of cardiac recipients who were treated with HD or PD reported an increased mortality rate with PD, although patients with increased volume sensitivity may...
have been directed to PD, biasing the results. We believe that HD or PD may be reasonable options to consider for organ transplant patients on a case-by-case basis. Better studies are needed before firm conclusions may be drawn about the relative benefits or hazards of PD in these populations.

**Simultaneous Solid-Organ Kidney Transplantation**

The issue of simultaneous solid-organ kidney transplantation frequently surfaces when nonrenal organ transplant candidates undergoing evaluation have concomitant kidney disease (Table 3). In the United States, >2800 multiorgan transplants involving a simultaneous kidney have been performed. Registry data indicate that the preponderance of kidney transplants involving a simultaneous liver-kidney transplant (SLKT), whereas a smaller proportion of SLKT donors kidney pool; (2) nonrenal organ recipients who progress to stage 5 CKD can subsequently be preemptively listed for sequential deceased donor kidney or undergo live-donor kidney transplantation, thereby minimizing or even avoiding eventual need for dialysis; and (3) purely from a deceased-donor organ use standpoint, kidneys that are placed into kidney-alone recipients have greater longevity than kidneys that are transplanted simultaneously with another organ.

The decision for SLKT should be based on multiple factors, including duration and degree of kidney dysfunction, potential for renal recovery after liver transplantation alone, and the impact of dual transplantation on recipient survival. By conventional criteria, current United Network for Organ Sharing regulations mandate that patients can be listed for kidney transplantation alone only once their estimated GFR is ""
requirement for chronic renal replacement therapy at 12 mo after liver transplantation.\textsuperscript{98} Using this approach, our rate of SLKT was 3\%, compared with 5\% nationally, whereas less than 1\% of recipients of a liver alone were on long-term dialysis at the end of the first posttransplantation year.\textsuperscript{98}

**Pharmacokinetic Interactions between CKD Medications and Immunosuppressants**

Monitoring for drug interactions with immunosuppressants typically falls under the purview of the transplant center. However, several medications that commonly are used by nephrologists in CKD management may have pharmacokinetic interactions with immunotherapies, with potential for catastrophic consequences for the transplanted organ. Examples include (1) non-dihydropyridine calcium channel blockers, which increase levels of CNI and sirolimus through inhibition of the Cyp3A enzyme system; (2) sevelamer, which reduces MMF exposure\textsuperscript{102}; and (3) statins, which have markedly increased exposure and potential for toxicity in the presence of CsA but not tacrolimus.\textsuperscript{103} We recommend that changes in the medication regimen of nonrenal organ recipients with CKD be promptly brought to the attention of the transplant team.

**DIRECTIONS FOR RESEARCH**

The escalating problem of CKD after nonrenal organ transplantation and the paucity of established therapies call for intense research efforts to identify strategies to prevent and treat this complication. Such research efforts may require focus on a single organ system, whereas others may be able to pool recipients of different solid organs.

**Innovations in Immunosuppression**

Given the impact of CKD on outcomes in this population, a major research objective is the development of effective immunosuppressive regimens that avoid kidney injury. Novel therapies that may offer freedom from CNI-mediated nephrotoxicity are under investigation in renal transplant patients, including belatacept, AEBO71, and CP-690-550. Assuming that safety and efficacy can be established in the kidney transplant setting, the investigation of these therapies among nonrenal organ transplant patients could represent a major advancement.\textsuperscript{104}

**Antifibrogenic and Anti-Inflammatory Therapies**

Experimentation with antifibrogenic and anti-inflammatory therapies can also take advantage of the existing mechanistic insights into the pathogenesis of CKD after solid-organ transplantation. Even at this time, an urgent need exists for systematic studies to evaluate the potential benefit of statins and RAAS blockade on preserving kidney function.

**CONCLUSION**

CKD after solid-organ transplantation is a burgeoning problem with devastating morbidity and mortality. Transplant professionals should understand the limitations of serum creatinine and estimating equations for renal function both in transplant candidates and in recipients. In addition, given strong evidence that AKI is an important risk factor for the development of CKD, every effort must be made to avoid nephrotoxic insults during the perioperative period of the organ transplant. In the absence of clinical trials for the prevention and treatment of CKD specifically among nonrenal solid-organ transplant recipients, we advocate for aggressive treatment of risk factors such as BP, as outlined in KDOQI. CNI minimization may also be an important approach to slowing progression to ESRD, although this decision must be balanced against the need to avoid rejection of the transplanted organ.

**DISCLOSURES**

R.D.B. has been a consultant for Roche, Novartis, Amgen, and Merck and has received research funding from Novartis.

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