# Long-Term Immunosuppression Management
## Opportunities and Uncertainties

*David Wojciechowski*[1] *and Alexander Wiseman*[2]

### Abstract
**The long-term management of maintenance immunosuppression in kidney transplant recipients remains complex. The vast majority of patients are treated with the calcineurin inhibitor tacrolimus as the primary agent in combination with mycophenolate, with or without corticosteroids. A tacrolimus trough target 5–8 ng/ml seems to be optimal for rejection prophylaxis, but long-term tacrolimus-related side effects and nephrotoxicity support the ongoing evaluation of noncalcineurin inhibitor–based regimens. Current alternatives include belatacept or mammalian target of rapamycin inhibitors. For the former, superior kidney function at 7 years post-transplant compared with cyclosporin generated initial enthusiasm, but utilization has been hampered by high initial rejection rates. Mammalian target of rapamycin inhibitors have yielded mixed results as well, with improved kidney function tempered by higher risk of rejection, proteinuria, and adverse effects leading to higher discontinuation rates. Mammalian target of rapamycin inhibitors may play a role in the secondary prevention of squamous cell skin cancer as conversion from a calcineurin inhibitor to an mammalian target of rapamycin inhibitor resulted in a reduction of new lesion development. Early withdrawal of corticosteroids remains an attractive strategy but also is associated with a higher risk of rejection despite no difference in 5-year patient or graft survival. A major barrier to long-term graft survival is chronic alloimmunity, and regardless of agent used, managing the toxicities of immunosuppression against the risk of chronic antibody-mediated rejection remains a fragile balance.**

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[1]Department of Medicine, University of Texas Southwestern Medical Center, Dallas, Texas
[2]Centura Transplant, Denver, Colorado

**Correspondence:** Dr. David Wojciechowski, Kidney Transplantation, University of Texas Southwestern Medical Center, 5959 Harry Hines Boulevard, POB 1, Suite 4.102E, Dallas, TX 75235, or Dr. Alexander Wiseman, Kidney Transplantation, Centura Transplant, 2525 S. Downing Street, Suite 380, Denver, CO 80210. Email: david.wojciechowski@utsw.edu or alexanderwisemanjr@centura.org

## Introduction
The long-term management of immunosuppression remains a tale of immediate gratification followed by frustrations and occasional disappointment. The introduction of calcineurin inhibitors and mycophenolate as immunosuppressive therapies began an era of improved maintenance immunosuppression efficacy. Short-term acute rejection rates decreased, and 1-year outcomes improved. Despite this short-term success, long-term kidney allograft survival has frustratingly not enjoyed a similar rate of improvement (1). In evaluating this discrepancy of short- versus long-term outcomes, it is apparent that the same maintenance immunosuppression that provides excellent short-term results may contribute to graft attrition with long-term exposure. In this review, we evaluate the current state of maintenance immunosuppression in kidney transplant recipients and discuss areas of opportunity and uncertainty in their long-term use.

## Ideal Calcineurin Inhibitor Targets
The current standard of care in kidney transplant immunosuppression in the United States has evolved to be a calcineurin inhibitor–based immunosuppression regimen with tacrolimus and mycophenolate. Over 90% of patients in the United States are maintained on these two agents, with or without steroids (2). This is largely attributed to the landmark Symphony trial, which demonstrated superior outcomes in terms of both acute rejection rates and GFR at 1 in 3 years using a tacrolimus-based regimen when compared with cyclosporin- or sirolimus-based regimens (3), and historical studies that support mycophenolate over azathioprine due to reductions in early acute rejection rates (4). However, there remains ongoing debate regarding the appropriate dose of tacrolimus and appropriate mycophenolate exposure for optimal immunosuppression in the long term. Importantly, in the Symphony trial, although tacrolimus trough (tacrolimus $C_0$) level goals were protocol specified at 3–7 ng/ml, the actual achieved tacrolimus $C_0$ exposure averaged 6.4 ng/ml at 12 months and 6.5 ng/ml at 36 months. Thus, a more appropriate interpretation of the Symphony trial is that a tacrolimus $C_0$ dose range of 5–8 ng/ml should be considered the standard of care.

Regarding mycophenolate exposure, attempts to define appropriate dose/exposure have not been fruitful, with the best attempt at defining optimal dose residing in the OPTICEPT trial in which a concentration-controlled dosing with reduced calcineurin inhibitor exposure was noninferior to standard calcineurin inhibitor/mycophenolate dosing for prevention of acute rejection (5). Compounding this lack of guidance is a paucity of data supporting improvements in graft or patient survival over time with mycophenolate compared with azathioprine (6).

  

No study to date has demonstrated superior outcomes with low-dose tacrolimus exposure <5 ng/ml (7,8). A number of recent studies lend support to maintenance of tacrolimus $C_0$ >5 ng/ml in the prevention of *de novo* DSA formation, a marker currently used as a surrogate for future alloimmune injury, chronic antibody needed rejection, and alloimmune graft loss (9). In a single-center study of 538 patients followed from 2007 to 2013 who were maintained on tacrolimus and mycophenolate, a mean tacrolimus $C_0$ <8 ng/ml was associated with *de novo* DSAs by 12 months (odds ratio, 2.32; 95% confidence interval [95% CI], 1.30 to 4.15; $P=0.004$), whereas tacrolimus time in the therapeutic range 5–10 ng/ml of <60% during the first year was associated with *de novo* DSA (odds ratio, 2.05; 95% CI, 1.28 to 3.30; $P=0.003$), acute rejection (hazard ratio [HR], 4.18; 95% CI, 2.31 to 7.58; $P<0.001$) by 12 months, and death-censored graft loss by 5 years (HR, 3.12; 95% CI, 1.53 to 6.37; $P=0.002$) (10). Another single-center analysis of 596 kidney transplant recipients found an independent relationship of mean tacrolimus $C_0$ <5 and HLA-DR/DQ eplet mismatch with *de novo* DSA development (11). After *de novo* DSA develops, a higher mean tacrolimus $C_0$ may protect against future graft loss (HR, 0.52; 95% CI, 0.30 to 0.89), with a threshold mean tacrolimus $C_0$ <5.3 ng/ml predictive of graft loss (12). Taken together, these data support recommendations to maintain tacrolimus $C_0$ >5 ng/ml for adequate immunosuppression.

Appropriate tacrolimus trough goals must be adjusted downward when using tacrolimus in combination with mammalian target of rapamycin (mTOR) inhibitors, such as everolimus or sirolimus, due to a synergistic nephrotoxic effect noted with this combination. In the TRANSFORM trial, 2037 subjects were randomized to reduced-dose tacrolimus (tacrolimus $C_0$ 2–4 ng/ml) in combination with everolimus or standard tacrolimus/mycophenolate–based immunosuppression (tacrolimus $C_0$ 6–10 ng/ml) (13). At 12 months post-transplant, no differences were noted between treatment arms for the combined end point of treated biopsy-proven acute rejection or eGFR<50 ml/min per 1.73 $m^2$ (48.2% in the everolimus arm versus 45.1% in the mycophenolate arm), graft loss, or death. There were fewer reported CMV and BKV events in the EVR arm, with higher discontinuation rates in the everolimus arm (23.0% versus 11.9%). Although this study suggests that one can achieve similar graft outcomes with a calcineurin inhibitor/mycophenolate–based regimen compared with a low-dose calcineurin inhibitor/everolimus regimen, longer-term kidney outcomes and *de novo* DSA formation were not evaluated, and different side effect profiles may make one strategy better suited for an individual patient.

## Noncalcineurin Inhibitor–Based Regimens

Despite the predominant use of calcineurin inhibitors in the United States as the primary immunosuppressant agent (2), they are accompanied by multiple off-target side effects. Calcineurin inhibitors are associated with a higher risk of post-transplant diabetes, elevated BP, worsening hyperlipidemia, neurotoxicity, and acute and chronic nephrotoxicity (14–22). Currently, only one calcineurin inhibitor–free regimen, belatacept in combination with mycophenolate and corticosteroids, is US Food and Drug Administration (FDA) approved for use in adult kidney transplant recipients seropositive for Epstein–Barr virus. Belatacept is a soluble fusion protein that binds to CD80 and CD86 on the surfaces of antigen-presenting cells, thereby inhibiting CD28-mediated T cell costimulation (23). The regulatory approval of belatacept was, in part, on the basis of the results from two randomized phase 3 trials: BENEFIT and BENEFIT-EXT (24–27). In these studies, two dosing regimens of belatacept ("more intense" and "less intense") were compared with a cyclosporin-based immunosuppression regimen. Under the FDA-approved "less intense" regimen, belatacept 10 mg/kg is administered intravenously on days 1 and 5 and weeks 2, 4, 8, and 12 post-transplantation, and 5 mg/kg belatacept is given every 4 weeks thereafter; outcomes with this dosing regimen are summarized below.

BENEFIT and BENEFIT-EXT differed primarily in the donor population that was utilized for transplantation. In BENEFIT, patients were transplanted with a living or standard criteria deceased donor kidney (26). At 12 months post-transplantation, the acute rejection rates for belatacept and cyclosporin were 17% and 7%, respectively; however, GFR was higher in the belatacept arm, even in those with rejection (mean measured GFR at month 12 in belatacept-treated patients with acute rejection was 61 versus 51 ml/min/ per 1.73 $m^2$ in cyclosporin-treated patients without acute rejection). Patients enrolled to BENEFIT-EXT were recipients of extended criteria donor kidneys, kidneys with an anticipated cold ischemia time ≥24 hours, or kidneys donated after cardiac death (24). At 12 months post-transplantation, 18% of patients randomized to belatacept and 14% of those randomized to cyclosporin experienced acute rejection.

Acute rejection episodes under belatacept-based treatment tend to occur early in the post-transplantation period, with a low incidence of late rejections (24,26), and few events are reported after month 12 (25,27). The acute rejection rates at 3 years post-transplantation among belatacept-treated and cyclosporin-treated patients in BENEFIT were 17% and 10%, respectively (27); the corresponding values in BENEFIT-EXT were 19% and 16%, respectively (25).

In analyses of BENEFIT performed at 7 years post-transplantation, belatacept-based immunosuppression was associated with a reduction in the risk of death or graft loss compared with cyclosporin-based immunosuppression (HR, 0.57; 95% CI, 0.35 to 0.94; $P=0.02$) (28), whereas in BENEFIT-EXT, the risk of death or graft loss at 7 years post-transplantation was similar between the groups (HR, 0.93; 95% CI, 0.63 to 1.36; $P=0.70$) (29). Despite the difference in acute rejection between belatacept and cyclosporin at 7 years, belatacept-based immunosuppression was associated with superior kidney function in both studies as eGFR maintained a positive slope and increased by +1.39 ml/min per 1.73 $m^2$ per year in BENEFIT and +1.51 ml/min per 1.73 $m^2$ per year in BENEFIT-EXT, with mean 7-year eGFRs of 63.3 and 54.2 ml/min per 1.73 $m^2$ in BENEFIT and BENEFIT-EXT, respectively. In contrast, eGFR decreased over time in the cyclosporin group by −1.04 ml/min per 1.73 $m^2$ per year in BENEFIT and −0.01 ml/min per 1.73 $m^2$ per year in BENEFIT-EXT (both $P<0.001$), with mean 7-year eGFRs of 36.6 and 35.3 ml/min per 1.73 $m^2$ for BENEFIT and BENEFIT-EXT, respectively (29,30). Additionally, patients treated with belatacept were noted to have lower

*de novo* DSA formation (31), lower BPs with fewer antihypertensive medications, better LDL control, and a lower incidence of post-transplant diabetes (32). Unfortunately, post-approval clinical experiences have been hindered by unacceptably high acute rejection rates that have dampened enthusiasm for more widespread use, and utilization remains well below 5% in the United States (33). Small studies have suggested that the optimal belatacept regimen may include lymphocyte-depleting induction in combination with an mTOR inhibitor instead of mycophenolate with or without corticosteroids (34–36).

## Calcineurin Inhibitor Conversion

In order to avoid early acute rejection while preserving kidney function in the long term, a number of calcineurin inhibitor conversion regimens have been explored using either belatacept or mTOR inhibitors as the primary immunosuppressive agent. For the former, in a randomized trial, 173 patients 6–36 months post-transplantation either were switched to belatacept ($n=84$) or remained on a calcineurin inhibitor–based regimen ($n=89$) (37). At month 12, the mean increases from baseline eGFR were $7\pm11.99$ ml/min per 1.73 $m^2$ in the belatacept group and $2.1\pm10.34$ ml/min per 1.73 $m^2$ in the calcineurin inhibitor continuation group. Patient and graft survival rates were 100% and 99% in the belatacept and calcineurin inhibitor groups, respectively. In the 2-year extension study, the mean changes in eGFR were 8.8 ml/min per 1.73 $m^2$ in the belatacept group and 0.3 ml/min per 1.73 $m^2$ in the calcineurin inhibitor group (38). If the differences in eGFR continue to persist, the improved kidney function seen with belatacept could translate into several additional years of allograft function.

mTOR inhibitors have been used as part of the *de novo* maintenance regimen to spare calcineurin inhibitor exposure as well as a conversion agent to eliminate calcineurin inhibitors. In the Symphony trial, kidney transplant recipients were assigned either to receive cyclosporin or tacrolimus combined with mycophenolate and steroids or to receive sirolimus, mycophenolate, and steroids. The worst results in terms of graft survival, biopsy-proven acute rejection, and eGFR were observed in the sirolimus groups (3). In the ORION trial, 443 patients with kidney transplants were randomized to sirolimus plus tacrolimus with tacrolimus elimination at week 13 (group 1), sirolimus and mycophenolate (group 2), or tacrolimus and mycophenolate (group 3) (7). Group 2 experienced a 1-year acute rejection rate of 31.3% and was sponsor terminated. The 1-year acute rejection rates for groups 1 and 3 were 15.2% and 8.2%, respectively. At 2 years, mean Nankivell GFR were not different among the 3 groups. At 1 and 2 years, there were no statistically significant differences in patient or graft survival between groups 1 and 3 or groups 2 and 3 (with data limitations noted for group 2) (7). Similar results have been reported with everolimus. In the ZEUS trial, 503 *de novo* kidney transplant recipients were enrolled. After initial treatment with basiliximab induction and maintenance cyclosporin, mycophenolate sodium, and corticosteroids, 203 patients were dropped from the study at 4.5 months because of adverse events and/or elevated values of serum creatinine or proteinuria. The remaining 300 patients were randomly assigned to replace cyclosporin with everolimus or to continue standard cyclosporin-based treatment (39). At 36 months, the everolimus regimen was associated with a significant improvement in kidney function with an eGFR of $67.9\pm21.6$ versus $60.6\pm16.4$ ml/min per 1.73 $m^2$ in the cyclosporin group ($P=0.01$). Rates of biopsy-proven acute rejection at 36 months were higher in the everolimus group (13%) than in the cyclosporin group (4.8%) after randomization ($P=0.02$). Patient and graft survival rates were similar between groups.

Late discontinuation of calcineurin inhibitors with mTOR inhibitor replacement has also been explored but with disappointingly mixed results. For example, in the CONVERT trial, 830 kidney allograft recipients treated with a calcineurin inhibitor 6–120 months post-transplant were randomly assigned to continue their calcineurin inhibitor or convert from calcineurin inhibitor to SRL (40). At 2 years, the rates of biopsy-proven rejection were 7.9% and 6.9% for patients on sirolimus and patients on calcineurin inhibitor, respectively. There was no difference in 2-year patient or graft survival. In patients converted to sirolimus, malignancy rates were significantly lower, but the cumulative number of side effects was significantly higher. Median proteinuria increased significantly after conversion to sirolimus. In patients with eGFR$<40$ ml/min at the time of randomization, kidney function tended to deteriorate earlier in the sirolimus group (40). Overall, the role of mTOR inhibitors to replace calcineurin inhibitors as part of a conversion strategy has been met with mixed results. Current data suggest that patients with an already reduced eGFR and/or proteinuria will receive no benefit (40) from calcineurin inhibitor elimination with mTOR inhibitor conversion, and early use of mTOR inhibitors without a calcineurin inhibitor may be mired by high rejection rates and a high side effect profile, thus potentially limiting their use.

There is some evidence supporting a role for mTOR inhibitors in reducing the risk of cancer, particularly skin cancer. The most common cancer in kidney transplant recipients is squamous cell carcinoma (SCC), with a 65- to 250-fold higher risk compared with the general population (41). The immunosuppression risk in SCC results from both a decrease in immune surveillance and drug-specific effects. Calcineurin inhibitors may enhance SCC development through mechanisms independent of host immunity (42,43). In contrast, some studies have noted a lower rate of SCC in transplant recipients treated with an mTOR inhibitor compared with those on a calcineurin inhibitor (44–46). In one multicenter randomized trial of kidney transplant recipients, the effect of conversion from a calcineurin inhibitor to the mTOR inhibitor sirolimus for secondary prevention of SCC versus staying on a calcineurin inhibitor was evaluated (47). New SCC developed in 22% and 39% of the sirolimus conversion group and the calcineurin inhibitor group, respectively ($P=0.02$), with a relative risk in the sirolimus group of 0.56 (95% CI, 0.32 to 0.98) despite a higher discontinuation rate. Graft function remained stable in the two groups. It should be noted that this benefit primarily extended to patients who experienced a single SCC event prior to conversion. The potential protective effects of mTOR inhibitors for malignancy must be balanced against the inferior graft outcomes noted with this agent, as evidenced by a large meta-analysis describing a 40% reduced risk of malignancy but a 43% higher risk of mortality with SRL use or conversion (48).

## Steroid Withdrawal

Early corticosteroid withdrawal (within the first week post-transplant) is a common immunosuppression strategy, as approximately 30% of all kidney transplant recipients are maintained on tacrolimus/mycophenolate steroid-free immunosuppression at 1 year following transplant in the United States (2). However, the long-term benefits (and risks) of steroid-free regimens are unclear. A well-performed randomized controlled trial with 5-year follow-up demonstrated no differences in graft or patient survival, cardiovascular risk factors, weight gain, or incidence of post-transplant diabetes, with more acute rejection in the early corticosteroid withdrawal arm and fewer bone complications in the steroid-containing arm (49). The increase in acute rejection rates in early corticosteroid withdrawal can be mitigated, but not entirely eliminated, by the use of depleting antibody induction (50). A number of registry analyses have corroborated the findings of a lower acute rejection risk when using depleting antibody therapy and a steroid-free regimen with acceptable short-term graft and patient survival (51–53); however, a recent registry analysis reported higher graft loss and mortality in deceased donor recipients with delayed graft function who underwent early corticosteroid withdrawal (54).

In a large meta-analysis of studies comparing steroid withdrawal versus steroid maintenance, the cumulative data reiterated this increase in acute rejection risk (seven studies, 835 participants: RR, 1.58; 95% CI, 1.08 to 2.30) but found no significant difference in 1-year patient mortality (ten studies, 1913 participants: RR, 0.68; 95% CI, 0.36 to 1.30), graft loss (eight studies, 1817 participants), or graft loss excluding death with functioning graft (RR, 1.17; 95% CI, 0.72 to 1.92) (55). There was no evidence to suggest a difference in harmful events, such as infection and malignancy.

Beyond these hard end points and examining other corticosteroid-associated complications, a single-center experience reported 15-year outcomes in 1553 patients transplanted from 1999 to 2015 utilizing an early corticosteroid withdrawal protocol (56). Compared with a historical cohort, nongraft-related complications (avascular necrosis, cytomegalovirus infection, cataract formation, new-onset diabetes after transplant, and cardiac complications) were significantly lower in the early corticosteroid withdrawal cohort. A single well-performed, prospective, randomized controlled trial of 615 patients with stringent diagnoses of post-transplant diabetes using current American Diabetes Association guidelines demonstrated equivalent acute rejection rates using depleting or nondepleting antibody induction therapy and significantly lower rates of post-transplant diabetes in early corticosteroid withdrawal (24%) versus continued corticosteroid therapy (39%) at 12 months (57). One potential explanation for the differences found in this trial compared with previous reports includes utilization of low–immunologic risk patients, primarily first transplant recipients with no sensitization (0% calculated panel-reactive antibodies) (57). Overall, the overwhelming evidence suggests that steroid withdrawal after kidney transplantation significantly increases the risk of acute rejection yet provides comparable short- and medium-term graft survival, but withdrawal has limited effect on traditionally considered steroid-related side effects. In the absence of more robust findings, early corticosteroid withdrawal will likely continue at the approximately 30% rate that it has maintained for the past decade (2).

## Balancing Risk of Chronic Alloimmunity with Chronic Nephrotoxicity

The problem of chronic alloimmunity (chronic antibody-mediated rejection) versus chronic nephrotoxicity has become the yin and yang of tacrolimus-based immunosuppression. The untoward effects of tacrolimus-based immunosuppression are perhaps best exemplified by a recent comprehensive surveillance biopsy study that described histologic injury 10 years after transplant in functioning grafts. In 145 surveillance biopsies performed 10 years following transplant, arteriolar hyalinosis, mesangial sclerosis, and global glomerulosclerosis were the most common lesions identified in 50%–70% of biopsies (58). These lesions generally are considered nonimmunologic in nature and often are associated with the systemic and vascular effects of calcineurin inhibitors. These findings are in contrast to prior studies of kidneys biopsied in a state of impending failure (mean 4.2 years following transplant) or "for cause" (with failure at a median 2.7 years following biopsy), in which glomerular lesions and antibody-mediated injury were the most common findings (59,60). In the short term, control of alloimmunity is critical, but the price to be paid for this control is later nephrotoxicity. Long-term transplant outcomes are clearly limited, at least in part, by adverse effects of calcineurin inhibitor–based immunosuppression, which has led to the search for minimization or withdrawal strategies as described above. Many have been reported, and although some result in improved kidney function, this is often at higher risk of rejection, best summarized by a comprehensive meta-analysis by Sawinski *et al.* (61). Perhaps a combination of low-dose tacrolimus in combination with angiotensin-converting enzyme inhibitor/angiotensin II receptor 1 blocker therapy may permit both adequate immunosuppression and protection from chronic scarring related to tacrolimus use. A recent randomized controlled trial supports this hypothesis, demonstrating that early low-dose tacrolimus exposure during the first 6 months post-transplant (tacrolimus $C_0$ target of $5\pm1$ versus $8–12\pm2$ ng/ml) together with angiotensin-converting enzyme inhibitor/angiotensin II receptor 1 blocker use demonstrated equivalent GFR, acute rejection rates, and *de novo* DSA rates compared with "standard" tacrolimus exposure, with reductions in interstitial fibrosis and tubular atrophy on surveillance biopsy at 24 months following transplant (62).

## Are There New Immunosuppression Agents on the Horizon?

At present, there is a paucity of novel maintenance immunosuppressive agents in the pipeline. Iscalimab, an anti-CD40 mAb, has been studied in a phase 2 trial, and other agents targeting costimulation blockade are in preclinical development (63). Clinicians are thus left to determine how best to optimize the agents currently available, including use of once-daily formulations of tacrolimus (64), alternative dosing strategies for belatacept (65), and risk assessment of patients (using both clinical and emerging immune

**Table 1. Examples of knowledge gaps in key clinical trials and potential next steps**

| Trial Name | Key Findings | Gaps/Opportunities | Future Strategies (Applicable to All Studies) |
|---|---|---|---|
| Symphony | Tacrolimus superior to cyclosporin or sirolimus for the end points of 1-yr acute rejection, GFR | Optimal MMF dose unknown<br>Using nondepleting induction, no DSA assessment | Risk stratify patients for enrollment into minimization/withdrawal studies not only on the basis of traditional clinical and immunologic risk factors but also on novel immunologic assessments (*e.g.*, baseline T cell reactivity, epitope matching) |
| TRANSFORM | Everolimus/low calcineurin inhibitor/prednisone is noninferior to standard calcineurin inhibitor/mycophenolate/prednisone | No long-term outcomes of DSA, proteinuria, GFR | |
| BENEFIT | Belatacept with superior GFR despite higher AR rates than cyclosporin | Control arm not standard of care | Investigate end points beyond 1 year graft survival, patient survival, rejection (*e.g.*, iBox, GFR, histological end points)<br>Utilize emerging biomarker assessments to risk stratify patients for enrollment and randomization to determine timing of protocol-specified immunosuppression change/increase/decrease, and as surrogate end points (*e.g.*, blood genomic profiling, molecular assessment of kidney transplant biopsy tissue, urinary chemokines and mRNA, blood donor–derived cellfree DNA) |
| Astellas corticosteroid withdrawal | Tacrolimus/mycophenolate with comparable graft survival and GFR despite higher AR than tacrolimus/mycophenolate/prednisone | Details regarding rejection and effect on outcomes not described<br>No DSA data or formal histologic assessments | |
| CONVERT | Calcineurin inhibitor to sirolimus conversion at 6–120 mo was associated with inferior outcomes in those with GFR<40 and proteinuria in those above GFR 40 | Randomized by GFR and not by histologic features (*e.g.*, IFTA with lack of glomerulosclerosis) | |
| ZEUS | Cyclosporin to everolimus conversion at 4.5 mo was associated with higher GFR but more rejection and higher discontinuation rate | No DSA data or formal histologic assessments | |
| BEST | Belatacept/early steroid withdrawal with depleting antibody induction was not superior to TAC/early steroid withdrawal | No long-term GFR follow-up or formal histologic assessments | |

MMF, mycophenolate; DSA, donor-specific antibody; AR, acute rejection; IFTA, interstitial fibrosis and tubular atrophy; TAC, tacrolimus.

monitoring tools) in whom deviation from standard immunosuppression is desired. Future studies will need to examine clinically important end points beyond 1-year graft and patient survival and 1-year rejection rates in order for new immunosuppression and immunosuppressive strategies to gain traction. For example, a comprehensive predictor of long-term survival has recently been proposed, the "iBox score," that includes histology, GFR, DSA, and other clinical characteristics that have been validated as tools to predict long-term graft survival (66). General considerations to advance our current knowledge and clinical practice are provided in Table 1.

Long-term immunosuppression management remains a balancing act, with efforts being made to maximize outcome (patient and graft survival) and minimize toxicity. Thus far, no immunosuppression regimen has proven to be without a potential pitfall. Efforts, however, are underway in the transplant community to take a more balanced approach to immunosuppression by utilizing tools, such as donor-derived cellfree DNA, gene expression profiling, and HLA matching/DSA monitoring, to achieve a personalized approach to long-term immunosuppression management. Randomized clinical trials utilizing these tools are needed to better elucidate their role in long-term patient care and outcomes.

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