Immunosuppression Minimization: Current and Future Trends in Transplant Immunosuppression

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The past decade has witnessed unprecedented advances in renal transplantation propelled by novel and effective immunosuppression drugs. The introduction of mycophenolate mofetil (MMF), tacrolimus, cyclosporine microemulsion, sirolimus, a new generation of monoclonal antibodies (the anti–interleukin-2 receptor blockers, daclizumab and basiliximab), and the depleting polyclonal biologic Thymoglobulin has provided transplant physicians with a wide choice in selecting effective immunosuppression regimens (1–5). The intensification of immunosuppression, however, results in over-immunosuppression–associated complications such as opportunistic infections and malignancies. This is exemplified by the emergence of a previously rare infection, BK virus nephropathy, which may account for irreversible graft loss in 3 to 5% of renal transplant recipients (6). The threat of malignancy is yet another risk confronting patients on long-term immunosuppression, reported to occur in up to 40% of patients by 20 yr after transplantation (7). Another factor limiting improvement in long-term outcome is the occurrence of cardiovascular disease, a major cause of death in renal transplant recipients (8,9). Many of the current immunosuppression drugs are associated with one or more risk factors that predispose to atherosclerotic cardiovascular disease. Of the current immunosuppressive agents in use, corticosteroids and calcineurin inhibitors (CNI) are the most pro-atherogenic drugs (9). The cardiovascular risk of sirolimus is unclear: it can induce hyperlipidemia, but it has also been shown to inhibit intimal and smooth muscle cell proliferation (10). The prospect for the Food and Drug Administration of newer and more effective maintenance drugs (cyclosporine microemulsion, tacrolimus, MMF, and sirolimus) now no longer support this notion (13–17). Two rigorous double blind randomized trials (one US and one global) of late steroid withdrawal, advantages and risks associated with total steroid avoidance, optimal concomitant immunosuppression, requirement for biologic induction therapy, and the role of immune monitoring. Withdrawal of corticosteroids has been arbitrarily considered late when implemented beyond 3 mo after transplantation and early within 7 d after transplantation. Late withdrawal of corticosteroids has been considered safer than early withdrawal although results from recent studies with the use of the newer and more effective maintenance drugs (cyclosporine microemulsion, tacrolimus, MMF, and sirolimus) no longer support this notion (13–17). Two rigorous double blind randomized trials (one US and one global) of late steroid withdrawal with concomitant maintenance therapy consisting of cyclosporine and MMF demonstrate both the potential risks and benefits of these immunosuppression strategies (18,19). The inclusion criteria for the US study were first transplant recipients on cyclosporine, MMF (dose 2 g/d) and prednisone, who had no history of previous rejection and had a serum creatinine <2.4 mg/dl (18). Patients who fulfilled these criteria at 3 mo posttransplantation were randomized to continue prednisone therapy or withdrawal from prednisone over 2 mo. Two hundred sixty-six patients were enrolled when the study was stopped because of excess rejection in the prednisone-withdrawal group. At 12 mo after transplantation, the acute rejection rate was significantly higher in the withdrawal group compared with the group on maintenance steroids (30.8% versus 9.8%). However, the high rejection rate in the steroid withdrawal group was predominantly the result of a significantly higher rejection rate in African-American patients withdrawn from prednisone (Figure 1). Despite the increased risk of rejection, steroid withdrawal was associated with metabolic benefits; patients withdrawn from steroids with functioning grafts at 6 mo had significantly lower cholesterol levels and required less use of antihypertensive drugs. In the global

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second trial (Europe, South Africa, Australia), 500 renal transplant recipients were randomized in a double blind steroid regimen for 6 mo with an unblinded 6-mo follow-up (19).

Table 1 shows the steroid regimen, rejection rate, and side effects of the two treatment arms. The investigators from these two trials concluded that late withdrawal of steroids with concomitant immunosuppression therapy consisting of cyclosporine and MMF may result in a slightly greater but acceptable risk of acute rejection (except in black patients) but is associated with a reduction in some corticosteroid-related side effects. Similar findings were reported from a randomized, open-label, parallel-group trial of corticosteroids withdrawal in patients treated with tacrolimus and MMF (20). The incidence of acute rejection at 6 mo in patients withdrawn from steroids 3 mo after transplantation \((n = 279)\) was 5.9% compared with 0.9% in patients who were maintained on steroids \((n = 277)\) (20). Recent strategies in corticosteroid minimization have favored immunosuppression regimens in which steroids are withdrawn very early after transplantation (usually in the first week) or completely avoided (14–17,21,22). The potential advantages of the newer approaches in corticosteroid sparing are listed in Table 2. Acute rejection in patients with short-term exposure (or avoidance) of steroids occurs early after transplantation when renal allograft recipients are monitored closely and frequently. In contrast, late corticosteroid withdrawal \((>3\) mo) is instituted at a time when the patients’ clinic visits are infrequent and the follow-up care may not be under the direct supervision of the transplant center. The design and the outcome of trials with early steroid withdrawal or avoidance are shown in Table 3. All these trials have in common the use of biologic induction therapy to provide more effective immunosuppression coverage in the early posttransplant period. It is evident that trials with corticosteroid minimization or avoidance are associated with excellent short-term outcome. Caution, however, should be used when these regimens are incorporated in clinical practice; these trials were less than rigorous with the infrequent use of controls, outcome based on statistically underpowered studies, and lack of long-term follow-up. Another unresolved issue is the optimum concomitant immunosuppression that allows for the safest and most effective corticosteroid minimization regimen. The maintenance drug combinations in use, cyclosporine-MMF, tacrolimus-MMF, cyclosporine-sirolimus, and more recently tacrolimus-sirolimus have not been tested against each other in the context of

![Figure 1. The cumulative incidence of biopsy proven acute rejection 3 mos after transplantation in African-American (AA) and non-AA patients maintained or withdrawn from prednisone. Adapted from reference 18.](image)

<table>
<thead>
<tr>
<th>Table 1. Outcome of a double blind comparison of two corticosteroids regimens plus MMF and cyclosporine</th>
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</thead>
<tbody>
<tr>
<td>Steroid Regimen</td>
</tr>
<tr>
<td>preop dose</td>
</tr>
<tr>
<td>postop dose</td>
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<tr>
<td>day</td>
</tr>
<tr>
<td>2 to 56</td>
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<tr>
<td>57 to 84</td>
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<tr>
<td>&gt;84</td>
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<tr>
<td>Acute Rejection</td>
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<tr>
<td>6 mo</td>
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<tr>
<td>12 mo</td>
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<tr>
<td>Mean BP at 12 mo</td>
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<tr>
<td>systolic (mmHg)</td>
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<tr>
<td>diastolic (mmHg)</td>
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<tr>
<td>Mean total cholesterol at 12 mo</td>
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<tr>
<td>Mean bone density at 12 mo</td>
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<td>L3</td>
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corticosteroid minimization. Finally, the safety and benefits of very early withdrawal versus complete avoidance of steroids have yet to be determined although steroids-free regimens have contributed to the success of islet cells transplantation (27). A study that may resolve this issue is the FREEDOM trial. In this study, 300 patients are being randomized to three treatment arms: no corticosteroids; 7 d of corticosteroid therapy; and standard maintenance corticosteroid therapy. All patients will be treated with two doses of basiliximab at day 0 and day 4, MMF, and cyclosporine. This trial started enrollment in 2003. In the interim, transplant physicians should consider using corticosteroid minimization regimens selectively for patients who are at high risk of complications from steroid therapy: (1) patients previously treated with corticosteroids; (2) children with low immunologic risk; (3) patients at risk for skeletal disease; (4) patients with atherosclerotic cardiovascular disease; (5) patients with susceptibility to metabolic disorders; or (6) obese patients. In summary, efforts to spare or eliminate corticosteroid therapy can be successful provided patients are carefully selected and closely monitored.

**Calcineurin Inhibitors Minimization Regimens**

The introduction of CNI in renal transplantation, cyclosporine 20 yr ago, and tacrolimus a decade later resulted in a dramatic decrease in acute rejection rates and improvement in graft survival. However CNI-based immunosuppression is associated with complications that result in posttransplant morbidities that may limit further improvement in long-term outcome (8,9). While nephrotoxicity has been amply documented and is frequently cited as the Achilles’ heel of the CNI representing toxicity-limiting efficacy, the proof of inexorable progression of CNI-induced nephrotoxicity remains controversial (28–31) In a recent review of data from the Scientific Registry of Transplant Recipients, Ojo et al. (30) reported that 15.7% of recipients of extrarenal organs developed renal insufficiency within 5 yr of transplantation. In contrast, a large study of 1663 renal transplant recipients, Burke et al. (31) found that the majority of patients tolerated long-term cyclosporine without progressive nephropathy; in fact, low doses of cyclosporine were associated with worse long-term outcome (31). In the recent 5-yr follow-up of the phase III cyclosporine versus tacrolimus trial, the median serum creatinine was unchanged or slightly improved (28). The importance of the level of renal function at 1 yr after transplantation as a risk factor for long-term graft outcome was recently highlighted in an analysis of data from the United Network of Organ Sharing registry by Hariharan et al. (32). Patients who had a serum creatinine of 1.5 mg/dl or lower at 1 yr (or had a <0.3 mg/dl rise in serum

### Table 2. Advantages of very early withdrawal or complete avoidance of corticosteroids in renal transplantation

- Acute rejection may occur early and be readily diagnosed and treated.
- The host’s immune response remains unmodified by the effect of chronic steroid therapy. (12,23,24)
- No interference by steroids of tolerogenic pathway
- Lack of steroid dependency
- Prevention of heightened immune response after discontinuation of steroids
- More effective prevention of steroids side effects. (25,26)

### Table 3. Design and outcome of newer and more aggressive corticosteroid sparing trials

<table>
<thead>
<tr>
<th>Design</th>
<th>Immunosuppression</th>
<th>Corticosteroid Regimens</th>
<th>Outcome</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Canadian single-arm open label multicenter trial (n = 57)</td>
<td>Daclizumab Induction; MMF-CsA</td>
<td>None</td>
<td>AR at 1 yr 25%</td>
<td>(14)</td>
</tr>
<tr>
<td>The “Stanford” Protocol single-center pediatric trial (n = 43)</td>
<td>Prolonged Daclizumab induction (for 6 mo); MMF-Tacrolimus</td>
<td>None</td>
<td>AR 5% at a mean follow-up of 16 ± 9 mo</td>
<td>(17)</td>
</tr>
<tr>
<td>Open label randomized multicenter trial (n = 83)</td>
<td>Basiliximab induction; MMF-CsA</td>
<td>Standard steroids (Dosage, mg: 500-250-125-65-30 then gradually taper to 5–10)</td>
<td>AR at 1 yr 19%</td>
<td>(15)</td>
</tr>
<tr>
<td>Open label single-center trial in living donor kidney transplantation (n = 51)</td>
<td>Thymoglobulin induction; MMF-CsA</td>
<td>5 days of steroids (Dosage, mg: 500-250-125-65-30)</td>
<td>AR at 1 yr 20%</td>
<td>(21)</td>
</tr>
<tr>
<td>Open label single-arm multicenter trial (n = 80)</td>
<td>Basiliximab induction; SRL-Tacrolimus</td>
<td>6 days of steroids (Dosage: 500 mg, 1 mg/kg, 0.5 g/kg × 2 days, 0.25 mg/kg × 2 days)</td>
<td>AR at 1 yr 13%</td>
<td>(21)</td>
</tr>
</tbody>
</table>

* CsA, Cyclosporine; MMF, Mycophenolate mofetil; SRL, Sirolimus; AR, Acute rejection.
creatinine of between 6 and 12 mo) had the best long-term graft outcome. Hence patients who develop renal dysfunction from CNI nephrotoxicity (or for that matter acute rejection) are at greater risk of having a shortened graft half-life. However, the concern with the long-term use of CNI extends beyond their effect on renal function to their adverse effect on survival from deaths due to cardiovascular disease and malignancy. The most common cause of graft loss long-term is death with a functioning kidney (33). In a recent single-center study, cardiovascular events and malignancy were the most common causes of death after 5 yr of transplantation in patients with a functioning kidney (8). While there are differences in the side effect profile between cyclosporine and tacrolimus, therapy with CNI contributes to several cardiovascular risk factors, including hypertension, hyperlipidemia, and metabolic abnormalities such as hyperglycemia and hyperuricemia (9). In addition, nephrotoxicity from CNI may also contribute to cardiovascular disease. A recent study by Meire-Kriesche et al. (34) of 58,900 adult renal transplant recipients registered in the US Renal Data System showed that renal function at 1 yr was strongly associated with the incidence of cardiovascular death independent of many risk factors for cardiovascular disease. The third important risk associated with CNI use is malignancy (35–38). Cyclosporine has been shown to promote cancer progression by a direct cellular effect independent on its effect on the host immune cells (36). The effect of the dosage of cyclosporine on malignancy was explored in a prospective, open label randomized study by Dantal et al. (38). Two hundred thirty-one patients were randomized 1 yr after transplantation to either the continued use of the standard dose of cyclosporine or reduced dose of cyclosporine. With a 66-mo follow-up period, 37 patients in the standard dose group and 23 in the low-dose group developed cancers ($P < 0.034$); two thirds of the cancers were skin cancers. However the low-dose cyclosporine regimen was associated with a higher risk of rejection. A confounding aspect of this study, however, was that it was conducted in the azathioprine era before the introduction of the more powerful antiproliferative agents, MMF and sirolimus. Withdrawal of CNI in patients treated with azathioprine and prednisone has been associated with a high incidence of rejection and graft loss (39). The introduction of the newer, more powerful antiproliferative agents has prompted renewed interest and experimentation with CNI-sparing regimens, as well as CNI-free regimens. The purpose of this review is to evaluate the safety and potential benefits of the recent CNI–sparing/avoidance trials in renal transplantation. CNI sparing is defined as the initial use after transplantation of a standard or low dose of CNI with subsequent withdrawal. CNI-avoidance protocols consist of immunosuppression regimens that completely avoid the use of CNI.

**Trials with CNI-Sparing Regimens**

Five large, prospective, multicenter trials have evaluated the safety and efficacy of CNI withdrawal after renal transplantation. The first was reported by Smak Gregoor et al. (40) and was designed as a prospective randomized study in primary transplant recipients treated with an immunosuppression regimen consisting of cyclosporine, MMF, and prednisone. The objective of this study was to assess the safety of withdrawal of cyclosporine (50% reduction for 2 wk before discontinuation) or prednisone at 6 mo after transplantation compared with the continuation of triple therapy (Figure 2). Eighteen months after

![Figure 2](image-url)  
*Figure 2. The immunosuppression regimen and outcome following randomization, drug withdrawal (cyclosporine or MMF), or continuation of triple therapy. CsA, Cyclosporine; MMF, Mycophenolate Mofetil; BPAR, biopsy-proven acute rejection. * $P = 0.0001$ and $P = 0.001$ versus triple therapy and steroid withdrawal, respectively.*
drug withdrawal, the patients withdrawn from cyclosporine had a significantly higher incidence of biopsy-proven rejection compared with the patients withdrawn from prednisone or maintained on triple therapy. The second study reported by Abramowicz et al. (41) is a European multicenter trial that enrolled 187 renal transplant recipients treated with triple therapy (cyclosporine-MMF-prednisone) and randomized at 3 mo to either cyclosporine withdrawal or to continue cyclosporine therapy. Cyclosporine withdrawal was gradual over 3 mo. The primary end point was creatinine clearance 6 mo after complete withdrawal of cyclosporine. In the per-protocol population (the withdrawal group), which excluded patients with acute rejections, there was a statistically significant increase in creatinine clearance (7.5 ml/min, \( P = 0.02 \)) and improvement in serum creatinine (−11 versus +4 \( \mu \)mol/L, \( P = 0.0003 \)). Reversible acute rejections, the majority of which were mild, occurred in nine cyclosporine withdrawal patients versus two cyclosporine continuation patients (10.6% versus 2.4% of each group, \( P = 0.03 \)), with no graft loss. The lower rejection rate following CNI withdrawal reported by Abramowicz et al. (41) may have been achieved because of the more gradual withdrawal of cyclosporine. The next two trials (42,43) were designed to evaluate the efficacy of a maintenance regimen of sirolimus-prednisone following cyclosporine withdrawal. These trials were conceived to minimize the enhanced nephrotoxicity that was observed when sirolimus was used in combination with full-dose cyclosporine (2). These two studies (the first conducted in the United States and Europe, and the second conducted globally minus United States) have slightly different design but the same underlying rationale: assessing the safety and the potential benefits of cyclosporine withdrawal from a sirolimus and steroid regimen. The specific design of each trial and the immunosuppressive regimens are shown in Figures 3 and 4. In both of these studies, cyclosporine was withdrawn gradually over a period of 1 mo. In the US-Europe trial, cyclosporine was withdrawn at the end of month 2 after transplantation only in patients who had been rejection free (82% of patients were eligible for cyclosporine elimination). The incidence of acute rejection at 1 yr was not statistically significant (18.6% versus 22.0%, respectively) between patients who continued therapy with cyclosporine versus patients who were withdrawn from cyclosporine. Patients withdrawn from cyclosporine experienced a significant increase in the calculated GFR (42). In the design of the global trial, cyclosporine could be withdrawn in patients who had previously had a rejection episode (provided it was not a Banff grade 3 rejection) (43). Patients were excluded from the study if they suffered an acute vascular rejection in the 4 wk preceding randomization or patients with poor renal function (serum creatinine > 4.4 mg/dl). The overall incidence of biopsy-confirmed acute rejection was 13.1% in the first 3 mo before the randomization period (Figure 4). After randomization, between months 3 and 12, patients withdrawn from cyclosporine had a significantly higher incidence of acute rejection compared to patients maintained on cyclosporine (9.8% versus 4.2%, \( P = 0.035 \); Figure 4). However, the cumulative rejection rate at 1 and 3 yr in the cyclosporine withdrawal group, although numerically higher, was not statistically significant (20.2% versus 13.5% and 20.5% versus 14.9%) than the group maintained on cyclosporine. The cyclosporine withdrawal group experienced a significant and sustained increase in calculated GFR soon after discontinuation of cyclosporine (Figure 5). In fact, on the basis of 3-yr data of continued improvement in renal function (as reflected by GFR and serum creatinine), the Food and Drug Administration on April 11, 2003, approved the use of sirolimus.
The more ambitious immunosuppression regimens completely avoid the use of CNI. These are obviously more experimental protocols and should be considered with caution, preferably within the context of rigorous trials. Two recent trials that have experimented with CNI-free regimens were reported by Vincenti et al. (45) and Kreis et al. (46) The first study was a multicenter US-Europe trial with an immunosuppressive regimen that consisted of induction therapy with the anti–IL-2R antibody, Daclizumab, and maintenance therapy with MMF and steroids (45). The rationale for CNI avoidance in this study was that the anti–IL-2R antibody by blocking IL-2 binding to its receptor, could be substituted for CNI that inhibit cytokine transcription, particularly in the early posttransplant period, when there is increased risk of rejection.

Figure 5. The calculated GFR in patients treated with cyclosporine, sirolimus, and prednisone (prior to randomization) and following randomization to either continuation of the triple therapy or elimination of cyclosporine (and remain on double therapy with sirolimus and prednisone). SRL, Sirolimus; CsA, Cyclosporine; P, prednisone. *Statistically significant results.

Among the important end points of this study are acute rejection below 20%. In an initial pilot study we evaluated a protocol consisting of daclizumab induction, MMF 2 g/d, and sirolimus (target blood levels, 10 to 20 ng/ml) (48). We enrolled nine primary renal transplant recipients in this study by Kreis et al. (46) utilized a CNI-free regimen combining two antiproliferative agents, sirolimus and MMF, in conjunction with steroids but without antibody induction therapy. At 14 European centers, cadaver renal allograft recipients were randomized to receive sirolimus (n = 40) or cyclosporine (n = 38) in an open label design. All patients received MMF 2 g/d and corticosteroid. The dosage of sirolimus and cyclosporine were concentration-controlled. At 12 mo, graft survival and patient survival were similar between the two treatment groups. The incidence of biopsy-proven acute rejection was 27.5% in the sirolimus arm versus 18.4% in the cyclosporine arm, not statistically different. The calculated GFR was consistently higher in the sirolimus-treated patients compared with cyclosporine. A major concern with this trial was the very high doses of sirolimus that were required to attain the target sirolimus blood levels (30 ng/ml for 2 mo and 15 ng/ml thereafter). In addition, 43% of patients in the sirolimus treatment group were discontinued from the protocol for a number of reasons. Thus, while this trial demonstrated the potential efficacy of a regimen combining two antiproliferative drugs in the absence of CNI, it fell short of being fully successful. The addition to this regimen of induction therapy with a biologic agent may improve its tolerability, decrease the dose and target sirolimus levels required to provide efficacy, and possibly reduce the acute rejection below 20%. In an initial pilot study we evaluated a protocol consisting of daclizumab induction, MMF 2 g/d, and sirolimus (target blood levels, 10 to 20 ng/ml) (48). We enrolled nine primary renal transplant recipients in this
protocol. At 3 mo, only one of nine patients had an episode of mild acute rejection. While the immunosuppression regimen was well tolerated, anemia and hyperlipidemia were the most common side effects. Two larger trials have tested a similar immunosuppression regimen in a prospective randomized design (49–50). Flechner et al. (49) treated 61 patients randomized to either cyclosporine or sirolimus with a protocol design consisting of induction therapy the chimeric anti–IL-2R antibody basiliximab, MMF, and steroids. At 1 yr, patient and graft survival were not significantly different between the two treatment groups. The sirolimus-treated patients had a rejection rate of 6.4% compared with 16.6% in the cyclosporine treatment group. At 6 and 12 mo, the sirolimus-treated patients had a significantly lower mean serum creatinine levels than the cyclosporine-treated patients, 1.29 mg/dl and 1.32 mg/dl versus 1.74 and 1.78 mg/dl, respectively (P = 0.008 and P = 0.004). At 1 yr, there were no significant differences in lipid levels between the two treatment groups. A multicenter trial initiated by the Mayo Clinic uses a similar design but with a different choice of induction, the depleting polyclonal agent Thymoglobulin, and tacrolimus instead of cyclosporine (50). The study will ultimately enroll 300 patients, and the interim results in 126 patients are shown in Table 4. The results of trials with the combination of the two antiproliferative agents, sirolimus and MMF, corticosteroids, and induction with a biologic agent allude that this immunosuppression regimen appears to be effective and could be considered an alternative option from CNI-based immunosuppression. However the long-term safety, tolerability, and cost-effectiveness of this regimen requires a more thorough analysis.

Several emerging CNI-free therapies are being developed for use in renal transplantation. These novel protocols avoid CNI because the mechanism of action of CNI (but not MMF or sirolimus) abrogates pathways of lymphocyte response to alloantigens that also block activation-induced apoptosis and the development of tolerance, relegating patients to a lifetime of immunosuppression therapy with considerable toxicities. The most promising therapy is co-stimulatory blockade with LEA29Y, a recombinant fusion receptor protein consisting of the extracellular domain of CTLA4 (which binds with high affinity to CD80 and CD86 and blocks co-stimulation signals required for T cell activation) linked to the constant region of IgG1, can induce tolerance (in rodents) or indefinite graft survival (in non human primates) (51–53). A large multicenter prospective randomized study is testing the efficacy and safety of a regimen consisting of chronic intermittent intravenous therapy with LEA29Y and maintenance immunosuppression consisting of MMF and corticosteroids versus a standard regimen of cyclosporine, MMF, and prednisone. This study finished enrollment of 227 patients in December 2002. The LEA29Y trial represents a paradigm shift in immunosuppression therapy.

**Table 4. Six months outcome of the Mayo Clinic randomized trial**

- Tacrolimus Arm (target level 15 ng/mL) n = 61
  - 6 rejection = 10%
- Sirolimus Arm (target level 15 ng/mL) n = 65
  - 11 rejections = 17%
- 19 Crossovers
- 12 SRL to Tac for wound complications, hyperlipidemia, polyoma, and rejections
- 7 Tac to SRL for post-transplant diabetes and polyoma

*SRL, Sirolimus; Tac, Tacrolimus.*
therapy; replacing orally administered CNI and their requirements for therapeutic drug monitoring with intermittent parenteral therapy (administered at monthly or every other month intervals). In the future, effective blockade of the co-stimulatory pathway with one or more biologic agents may render unnecessary both the use of CNI and corticosteroids. A recently published study by Adams et al. (54) showed that Rhesus monkeys that underwent pancreaticectomy were successfully transplanted with allogeneic islet cells with an immunosuppression therapy that consisted of short induction with an anti-IL-2 antibody, chronic intermittent administration of LEA29Y and sirolimus. Until these experimental therapies fulfill their promise in clinical trials, clinicians have flexibility at the present time to individualize immunosuppression therapy and selectively consider corticosteroids or CNI sparing regimens for patients who could benefit from drug minimization.

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