Immunosuppressive Strategies to Improve Outcomes of Kidney Transplantation

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Summary: The introduction of several immunosuppressive agents over the past decade has reduced the rate of acute rejection significantly and has improved short-term renal allograft survival. However, their impact on long-term outcomes remains unclear. Current immunosuppressive strategies are focused on improving long-term graft and patient survival along with maintaining allograft function. The approval of the new immunosuppressive agents: rabbit antithymocyte globulin, basiliximab, daclizumab, tacrolimus, mycophenolate, and sirolimus, also has facilitated the development of steroid- and calcineurin inhibitor–sparing regimens in kidney transplantation. We discuss the impact of various immunosuppressive regimens on the outcome measures of kidney transplantation: acute rejection episodes, allograft survival, and renal function.

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The introduction of several new immunosuppressive agents into clinical practice over the past decade has reduced the incidence of acute rejection but their impact on long-term outcomes of kidney transplantation is unclear. Current immunosuppressive strategies focus on reducing adverse effects and improving renal function to prolong graft survival. As the use of these immunosuppressants evolves, the complexity of immunosuppressive protocols has increased. In this review, we discuss the impact of various combination regimens of immunosuppressants that have been approved over the past decade, including steroid and calcineurin inhibitor (CNI) withdrawal and avoidance protocols. Outcome measures are described in terms of acute rejection episodes, renal function, and allograft survival.

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RENAL ALLOGRAFT SURVIVAL BETWEEN 1990 AND 2005

Analysis of the US Scientific Registry of Transplant Recipients data from more than 62,000 adults who received a first kidney transplant between 1995 and 2000 showed that the acute rejection rates decreased from 35.7% to 14.6% in the 0- to 6-month posttransplantation period, from 21.4% to 6.2% in the 6- to 12-month period, and from 22.5% to 2.9% in the 12- to 24-month period.[1] Overall, the 6-year graft survival rates were similar for patients without acute rejection compared with those who experienced acute rejection with near-complete recovery of baseline renal function (74.4% versus 72.7%, respectively). In contrast, in patients with acute rejection and less than complete recovery of baseline renal function, graft survival rates were lower and declined in proportion to the degree of renal function impairment.[1]

Results of a single-center study of 429 patients who underwent transplantation between 1990 and 2000 showed that renal allograft function may be showing some improvement.[2] A pooled data analysis of 10,278 renal allograft recipients transplanted between 1984 and 2002

in 5 centers showed an improvement in the rate of decline in allograft function in the cohort transplanted between 1999 and 2002.[3] Similarly, analysis of data from 40,164 kidney transplant recipients between 1991 and 2000 from the United Network for Organ Sharing database showed an improvement in the 6-month estimated glomerular filtration rate (GFR) from 50 mL/min in 1991 to 55 mL/min in 2000.[4]

Despite considerable improvement in the rates of acute rejection and early graft failure during the past 20 years, the rate of late graft failure has remained relatively constant.[5] Analysis of actual versus projected half-lives for patients who underwent kidney transplantation between 1988 and 1995 showed no improvement in long-term allograft survival: the allograft survival being stable at 8 years.[5] Factors that are not fully elucidated at this time along with increased age of recipients and donors, increased waiting time to transplantation, and perhaps nephrotoxicity of CNIs, likely play a part in the failure to see a commensurate improvement in graft survival as compared with the improvements in preventing acute rejection.

INDUCTION IMMUNOSUPPRESSION

The rationales for induction immunosuppression are to provide intense immunosuppression in the early posttransplant period to prevent acute rejection. More recently, induction therapy with antibodies has been used in steroid- and CNI-sparing protocols.[6] Both lymphocyte-depleting antibodies (antithymocyte antibodies, OKT3, and aleutuzumab) and non–lymphocyte-depleting antibodies (interleukin-2 [IL-2]–receptor antibodies) have been studied.

Antilymphocyte Antibodies

In a 12-month, multicenter, open-label, randomized, prospective study of 309 kidney recipients comparing induction therapy with Thymoglobulin (Genzyme Corporation, Cambridge, MA) (n = 151) followed by initiation of tacrolimus on postoperative day 9 versus immediate tacrolimus-based immunosuppression (n = 158) with azathioprine and steroids, the incidence of steroid-sensitive acute rejection was lower in the induction than the noninduction group: 7.9% versus 22.2% (P = .001).[7] There was no difference in the rate of steroid-resistant acute rejection between the 2 groups. The 12-month allograft survival rate was similar between the 2 groups: 96.8% versus 91.1%. The mean serum creatinine level was 133.2 μmol/L (1.51 mg/dL) and 135.5 μmol/L (1.54 mg/dL) in the induction and noninduction groups, respectively.[7] However, higher rates of fever, cytomegalovirus (CMV), herpes simplex infection, leucopenia, thrombocytopenia, and serum sickness were observed in the induction group. Thymoglobulin, a rabbit-derived antithymocyte globulin, has replaced the horse-derived ATGAM (Pharmacia & UpJohn Company [Pfizer Inc.], Kalamazoo, MI). Compared with ATGAM, Thymoglobulin was more effective in preventing acute rejection.[8] The incidence of acute rejection was 8% versus 34% in the Thymoglobulin and ATGAM groups, respectively. The corresponding 5-year allograft survival rate was 77% and 55% in the Thymoglobulin and ATGAM groups, respectively.[8]

IL-2–Receptor Antibodies

The 2 IL-2 receptor antibodies, basiliximab (chimeric monoclonal antibody)[9-12] and daclizumab (humanized monoclonal antibody),[13,14] have been shown to reduce the incidence of acute rejection in kidney transplant recipients who received cyclosporine and steroids with[11,13] or without azathioprine[9,10,14] or mycophenolate mofetil (MMF).[12] In a meta-analysis of 8 randomized trials (4 basiliximab, 2 daclizumab, 1 anti-Tac, and 1 BT563 trials) of 1,871 kidney transplant recipients on a cyclosporine-based regimen, addition of IL-2–receptor antibodies reduced acute rejection episodes at 6 months by 49% (odds ratio, .51; 95% confidence interval, .42-.63).[15] However, there was no difference in the rate of graft loss and mortality at 12 months compared with placebo. There was also no increase in overall infection and CMV infection episodes.[15]

Several trials compared the efficacy of IL-2–receptor antibodies with antithymocyte antibodies in recipients receiving cyclosporine, MMF, and steroids.[16-20] In 105 kidney transplant recipients of low to normal immunologic risks,

rabbit antithymocyte globulin and basiliximab were equally effective in reducing the rate of acute rejection: 9.4% versus 9.6%%, respectively.[16] There was no difference in the 1-year patient and graft survival rate between the 2 groups: 98.1% and 94.2%, respectively, in the basiliximab group versus 98.1% and 96.2%, respectively, in the antithymocyte globulin group. Similar results were found in a French multicenter study of 100 patients of low immunologic risk who were randomized to receive rabbit antithymocyte globulin and basiliximab[17] and another multicenter study of 135 patients comparing ATGAM with basiliximab.[18] In patients with high immunologic risk, Thymoglobulin induction was associated with a significantly lower rate of acute rejection, 15.6% versus 25.5% in the basiliximab group.[19] Nonetheless, there was no difference in 1-year graft and patient survival. No difference in graft outcomes also was found in a group of 88 African American patients randomized to receive either rabbit antithymocyte globulin or basiliximab.[20] In most of these studies, basiliximab was associated with a lower incidence of CMV infection and bone marrow suppression. Interestingly, the Thymoglobulin Induction Study Group reported a lower incidence of CMV infection with Thymoglobulin compared with basiliximab (7.8% versus 17.5%, $P = .02$), although Thymoglobulin was associated with a higher incidence in overall infection (85.8% versus 75.2%, $P = .03$).[19]

Preliminary findings of 90 kidney transplant recipients who received tacrolimus, MMF, and steroids and were randomized to either Thymoglobulin, atelezumab, or daclizumab showed no difference in the incidence of acute rejection and 12-month creatinine clearance with a median follow-up period of 15 months.[21] In summary, studies to date have shown that induction therapy with the earlier-mentioned antibodies can reduce early acute rejection rates. The issue of risk/benefit for the long-term remains unanswered.

MAINTENANCE IMMUNOSUPPRESSION

CNIs

CNIs remain the cornerstone agent of the maintenance immunosuppressive regimen. Since 2000, more kidney transplant recipients received tacrolimus than cyclosporine.[22] A prospective study of 557 patients randomized to receive either tacrolimus or cyclosporine microemulsion showed that the incidence of acute rejection in the first 6 months posttransplantation was lower in the tacrolimus group (20% versus 37%, $P < .0001$), but there was no significant difference in graft survival at 2 years posttransplant.[23] The long-term follow-up results of the phase III trial reported by the Prograf Study Group showed no difference in the 5-year graft survival between tacrolimus- and cyclosporine-treated kidney transplant recipients: 64.3% and 61.6%, respectively.[24] However, the mean serum creatinine concentration was lower in the tacrolimus group: 123 μmol/L (1.4 mg/dL) versus 150 μmol/L (1.7 mg/dL) ($P = .0014$). There was a significantly higher rate of cross-over in the cyclosporine group because of an increased rate of refractory rejection episodes: 27.5% of cyclosporine-treated patients were switched to tacrolimus compared with 9.3% of tacrolimus-treated patients who were switched to cyclosporine.[24]

In a multicenter, prospective, randomized study involving 2 MMF-based maintenance immunosuppressive regimens, the incidence of acute rejection at 1 year was 15% (tacrolimus group) versus 20% (cyclosporine group).[25] There was no difference in renal function and 1-year graft survival between the 2 groups. At 2 years, the mean serum creatinine concentration was 138 μmol/L (1.57 mg/dL) versus 114 μmol/L (1.3 mg/dL), respectively.[26] The median GFR at 3 years was 59.3 mL/min in patients receiving tacrolimus versus 56.1 mL/min in those receiving cyclosporine.[27] By using a paired-kidney analysis of deceased donor kidneys from the Scientific Registry of Transplant Recipients database (one kidney transplanted to a recipient who initially was treated with tacrolimus and the contralateral kidney from the same donor transplanted to a patient initially treated with cyclosporine microemulsion), the 5-year graft survival was 66% in tacrolimus-treated recipients versus 67% in those who received cyclosporine microemulsion.[28] There was no difference in patient survival rate between the 2 groups. The aforementioned stud-

ies indicated that good outcomes can be achieved with either CNI. Evidence does exist that tacrolimus may be associated with better renal function than cyclosporine.

Antiproliferative Agents

MMF, an inosine monophosphate dehydrogenase inhibitor, was shown to be effective in preventing acute rejection after kidney transplantation when added to a CNI-based regimen. Compared to placebo in kidney transplant recipients receiving cyclosporine and prednisone maintenance therapy with no antibody induction, the incidence of acute rejection at 6 months was reduced from 46.4% (placebo group) to 17% and 13.8% in patients receiving MMF 2 g/day and 3 g/day, respectively.[29] Similarly, the Tri-continental MMF Renal Transplant Study Group showed that in patients who received cyclosporine, azathioprine, and prednisone and no antibody induction, substituting azathioprine with MMF reduced the incidence of acute rejection at 6 months from 35.5% (azathioprine) to 19.7% (MMF 2 g/d) and 15.9% (MMF 3 g/d), respectively.[30] Results from the US Renal Transplant MMF Study Group showed that substitution of azathioprine with MMF in patients who received antithymocyte globulin induction and cyclosporine, azathioprine, and prednisone maintenance therapy also reduced the 6-month acute rejection rates from 38% (azathioprine) to 19.8% (MMF 2 g/d) and 17.5% (MMF 3 g/d).[31]

A pooled analysis of combined data from these 3 multicenter, randomized, controlled trials in 1,493 kidney transplant recipients showed a reduced proportion of patients with acute rejection in the first year posttransplantation: 19.8% (MMF 2 g/d) versus 16.8% (MMF 3 g/d) versus 40.8% (azathioprine).[32] The rate of graft loss at 1 year was 9.6%, 10.8%, and 12.4% in patients receiving MMF 2 g/d, MMF 3 g/d, and azathioprine, respectively. The relative risk for first-year graft loss was 0.46 and 0.38 in patients receiving MMF 2 g/d and 3 g/d, respectively.[33] However, the long-term follow-up study of the European trial showed no difference in the rates of graft loss at 3 years: 15.2% (MMF 2 g/d) versus 18.8% (MMF 3 g/d) versus 22% (placebo).[34] Similarly, the US Renal Transplant MMF Study Group showed no difference in the 3-year graft loss rates between patients who received cyclosporine, MMF, and prednisone compared with those who received cyclosporine, azathioprine, and prednisone.[34] Ojo et al[35] assessed the risk for acute rejection in 66,774 patients who received either azathioprine or MMF and found that patients treated with MMF had a 15.5% incidence of rejection versus 24.7% in azathioprine-treated patients. The 4-year graft survival was 85.6% versus 81.9% (MMF versus azathioprine, $P < .0001$) and the 4-year patient survival was 91.4% versus 89.9% (MMF versus azathioprine, $P = .002$).[35] Meier-Kriesche et al[36] evaluated 49,666 patients who received their first renal allograft between 1988 and 1998. By using the reciprocal creatinine measurement as a marker for renal function and defining an event as a 20% decrement in renal function, MMF was associated with fewer events and hence longer-term allograft survival than azathioprine. The effect was notably strong in African Americans, with a 3-year death-censored graft survival of 85.8% in MMF-treated patients compared with 75.1% in azathioprine-treated patients.[36]

Sirolimus, a mammalian target of rapamycin inhibitor, is another antiproliferative agent that was approved in the late 1990s. Results of a phase III, multicenter, randomized, placebo-controlled study of 576 kidney transplant recipients comparing sirolimus with placebo added to a baseline cyclosporine microemulsion and prednisone regimen showed that the incidence of biopsy-confirmed acute rejection episodes was significantly lower in patients who received sirolimus 2 mg/d (24.7%) and 5 mg/d (19.2%), compared with those who received placebo (41.5%).[37] In another phase III, multicenter, randomized, double-blind study of 719 kidney transplant recipients comparing sirolimus with azathioprine in combination with a baseline cyclosporine microemulsion and prednisone regimen, the incidence of biopsy-proven acute rejection episodes was significantly lower in patients who received sirolimus 2 mg/d (16.9%) and 5 mg/d (12%) compared with those who received azathioprine (29.8%).[38] However, the serum creatinine concentration at 12 months was significantly higher in the sirolimus groups

than the azathioprine group, 160 μmol/L (1.8 mg/dL), 171 μmol/L (1.9 mg/dL), and 133 μmol/L (1.5 mg/dL), respectively. The 12-month graft survival was similar among the groups: 97.2%, 96%, and 98.1%, respectively.[38]

The Prograf Study Group reported the 1-year results of a randomized, multicenter, clinical trial comparing the combination of sirolimus or MMF with tacrolimus-based immunosuppression in kidney transplant recipients.[39] The incidence of biopsy-proven acute rejection at 6 months was 11.4% in the MMF group versus 13.0% in the sirolimus group. One-year patient and allograft survival rates were similar in both groups.[39] However, the mean serum creatinine concentration at 1 year was significantly higher in the sirolimus group: 150 μmol/L (1.7 mg/dL) versus 132 μmol/L (1.5 mg/dL) ($P = .03$) and almost twice as many sirolimus recipients had serum creatinine levels greater than 2 mg/dL: 20.4% versus 11.0% ($P = .02$).

The increased nephrotoxicity associated with the sirolimus and CNI combination regimens also is corroborated by registry data analyses. Evaluation of 24,000 kidney recipients transplanted between 1998 and 2003 showed that the Neoral (Novartis Pharmaceuticals Corporation, East Hanover, NJ)/sirolimus combination was associated with a higher rate of decline in renal function, lower graft survival (75% versus 79% at 4 years, $P = .002$), and death-censored graft survival (84% versus 87%, $P = .003$) compared with the Neoral/MMF combination.[40] Similarly, analysis of data in a separate cohort of 45,000 recipients transplanted between 2000 and 2004 showed that patients maintained on the sirolimus/tacrolimus combination had a lower overall and death-censored graft survival compared with those who received the tacrolimus/MMF combination.[41] At this point in time, combination therapy with a CNI and mammalian target of rapamycin inhibitor are difficult to justify given the number of other regimens available.

Corticosteroid-Sparing Regimens

Earlier attempts to withdraw steroids during the cyclosporine and azathioprine era showed a high rate of acute rejection.[42] The introduction of IL-2–receptor antibodies, tacrolimus, MMF, and sirolimus has rekindled the interest in designing protocols to eliminate steroids. The Collaborative Transplant Study reported the 7-year outcome of 1,015 patients who underwent steroid withdrawal at no earlier than 6 months posttransplant using a variety of protocols.[43] Graft and patient survival was 82% and 89%, respectively, in the steroid-withdrawn group compared with 75% and 84%, respectively, in retrospectively matched controls who continued to receive corticosteroids. The rate of acute rejection episodes in the steroid-withdrawn group was only 8%.[43] In a 6-month, multicenter, randomized European study, patients received tacrolimus (trough levels, 5-15 ng/mL), mycophenolate 1 g/d, and prednisone 10 mg/d for 3 months.[44] At 3 months posttransplant, 277 patients continued the triple immunosuppressive regimen, 279 discontinued steroids, and 277 discontinued mycophenolate. There was no difference in the incidence of acute rejection at 6 months among the 3 regimens, ranging from 14.8% to 17%.[44] The mean serum creatinine concentration at 6 months was 131.8 μmol/L (1.49 mg/dL), 138.8 μmol/L (1.57 mg/dL), and 138.3 μmol/L (1.56 mg/dL) in patients receiving triple therapy, tacrolimus and MMF, and tacrolimus and prednisone, respectively.[44]

Early corticosteroid withdrawal (5 days posttransplant) among renal transplant recipients receiving basiliximab induction and daily treatment with cyclosporine microemulsion and MMF was studied in 83 patients.[45] The incidence of biopsy-proven acute rejection at 12 months was not significantly different between the steroid-withdrawal group (20%) and the standard treatment group (16%). Patient and graft survival was 100% in the steroid-withdrawal group, although 1 patient died with a functioning allograft in the standard steroid group.[45] There was no difference in renal function at 12 months between the 2 groups: serum creatinine concentration was 123 μmol/L (1.4 mg/dL) versus 132 μmol/L (1.5 mg/dL) in the rapid withdrawal and the standard steroid group, respectively. At 6 months posttransplant, 72% of patients in the steroid-withdrawal group remained off steroids.[45]

By using a different IL-2–receptor antibody, Rostaing et al conducted a 6-month, randomized,

multicenter study of 538 kidney transplant recipients who received a regimen of either daclizumab, tacrolimus, mycophenolate, and an induction dose of methylprednisolone, or tacrolimus, mycophenolate, and a standard regimen of steroids.[46] The incidence of biopsy-proven acute rejection and steroid-resistant acute rejection were 16.5% and 5%, respectively, in both groups.

A pilot study of 51 live kidney recipients at the University of Minnesota using Thymoglobulin induction and 5 days of perioperative steroids with cyclosporine and MMF maintenance immunosuppression showed no significant difference in the 12-month actuarial patient survival, graft survival, and rejection-free graft survival compared with historical controls receiving cyclosporine-based steroid maintenance regimens with no induction treatment.[47] The mean serum creatinine concentration at 1 year was 150 μmol/L (1.7 mg/dL). The same group of investigators reported their 3-year experience in 349 recipients of live or deceased kidneys using a similar rapid steroid-withdrawal protocol that included Thymoglobulin, tacrolimus, or cyclosporine, and either mycophenolate or sirolimus.[48] The 3-year actuarial graft survival was 93% and the incidence of acute rejection was 8%. The mean serum creatinine concentration at 2 years was 141 μmol/L (1.6 mg/dL).[48] By using a similar protocol in 79 patients considered to be at high immunologic risk (high panel reactive antibodies, re-transplantation, or delayed graft function), Khwaja et al[49] reported a 94% 3-year actuarial graft survival.

Kandaswamy et al[50] reported their experience of 3 steroid-free maintenance immunosuppressive regimens. Steroids were withdrawn on the fifth postoperative day in 239 patients who received Thymoglobulin and then were maintained on either cyclosporine and MMF, or tacrolimus and sirolimus. At 2 years posttransplant, the rates of graft survival and acute rejection-free graft survival were approximately 95%, with no difference among the groups.[50] The mean serum creatinine concentration at 24 months was higher in the cyclosporine/MMF group. Overall, 83% of patients remained off steroids: 75% cyclosporine/MMF, 90% (high tacrolimus/low sirolimus), and 83% (low tacrolimus/high sirolimus).[50] At 48 months, the acute rejection-free graft survival was 86% and 80% in live and deceased kidney recipients, respectively.[51] The mean serum creatinine concentration was 141 μmol/L (1.6 mg/dL) at 1 year and 150 μmol/L (1.7 mg/dL) at 5 years. The 5-year patient- and death-censored allograft survival for the cohort was 91% and 92%, respectively.[51] Eighty-six percent of patients remained off steroids.

Kumar et al[52] reported their experience with the use of basiliximab induction with CNI (tacrolimus or cyclosporine) and MMF or sirolimus maintenance immunosuppression in 103 African American transplant recipients after 2 days of perioperative steroids. Compared with a matched group of 103 non–African American recipients, no differences in the rate of acute rejection, patient survival, and graft survival at 1 year were found. However, an increased incidence of subclinical acute rejection was noted in the African American recipients. A 3-year follow-up study from the same center using the same 2-day steroid withdrawal protocol in 150 transplant recipients (52% African American) showed a similar rate of acute rejection compared with 150 patients (56% African American) who received standard steroids, 16% versus 14%, respectively.[53] There was also no difference in the 3-year actuarial graft survival (78% and 79%, respectively) and renal function: the mean serum creatinine concentration was 167 μmol/L (1.9 mg/dL) and 158 μmol/L (1.8 mg/dL), respectively.[53] Early steroid withdrawal is gaining increasing favor; although short-term results are promising, the risk/benefit will require longer follow-up evaluation.

CNI-Withdrawal Regimens

The introduction of MMF- or sirolimus-based regimens has made it feasible to withdraw CNI from maintenance immunosuppression and improve renal function without a significant increase in acute rejection episodes. A Dutch study of 212 kidney transplant recipients who received cyclosporine, MMF, and steroids were randomized at 6 months after transplantation to continue on the same regimen (n = 73), withdraw from cyclosporine (n = 63), or stop prednisone (n = 76).[54] No induction therapy was

given. Patients were followed up for up to 2 years posttransplantation. Biopsy-proven acute rejection occurred in 22% after cyclosporine withdrawal compared with 4% in the prednisone-withdrawal group ($P = .001$) and 1.4% in the control group ($P = .0001$).[54] There was no difference in patient and graft survival among the groups but patients who successfully withdrew cyclosporine had a significantly lower serum creatinine concentration during follow-up evaluation.

Similar results were reported in 108 patients who were maintained on triple therapy with cyclosporine, MMF, and steroids for 3 months posttransplantation.[55] Thereafter, patients were randomized to either stop cyclosporine (MMF group) or MMF (cyclosporine group).The MMF group experienced a higher incidence of acute rejection: 22.2% versus 5.5%, and a lower 2-year graft survival: 93% versus 98% in the cyclosporine group.[55] There was also a higher incidence of complement fragment C4d deposition on protocol biopsy specimens in the MMF group irrespective of prior acute rejection. However, the MMF group had a sustained improvement in renal function at 1 (49.1 versus 40.1 mL/min/1.73 m^2) and 2 years (45.6 versus 37.3 mL/min/1.73 m^2) compared with the cyclosporine group.[55] In another multicenter prospective trial, 84 kidney transplant recipients who had a stable creatinine concentration on triple therapy with cyclosporine microemulsion, MMF, and prednisone were randomly assigned at 3 months posttransplant to withdraw from either cyclosporine or MMF.[56] Acute rejection episodes appeared more frequently in patients receiving MMF and prednisone (11.5% versus 5%, not significant). There was no difference in patient and graft survival between the 2 groups.[56] However, patients withdrawn from cyclosporine had better creatinine clearance: 71.7 mL/min versus 60.9 mL/min.

In a 5-year, prospective, randomized study evaluating cyclosporine withdrawal from a mycophenolate-based regimen, 77 patients were maintained on cyclosporine, mycophenolate, and corticosteroids and 74 patients had cyclosporine weaned over 12 weeks.[57] During the 4 years of follow-up evaluation, 7 of 74 patients in the MMF group versus 1 of 77 patients in the triple therapy group experienced acute rejection episodes ($P = .028$). There was a trend toward improved creatinine clearance in the MMF group: 67.4 mL/min versus 61.7 mL/min, $P = .05$.[57] The 4-year patient and graft survival for those who continued cyclosporine was 95% and 92%, respectively, compared with 93% and 88%, respectively, for those who were withdrawn from cyclosporine. Similarly, the 3-year follow-up evaluation of the Cyclosporine Avoidance Eliminates Serious Adverse Renal-toxicity (CAESAR) study, which evaluated the effects of reduction or withdrawal of cyclosporine in more than 300 de novo renal allograft recipients, also showed a higher rate of acute rejection in the cyclosporine-withdrawal group: 36% compared with 26% and 27% in the low- and normal-dose cyclosporine groups, respectively.[58] There was no difference in 3-year renal function, patient survival, and allograft survival among the groups. Hence, kidney transplant recipients whose cyclosporine was discontinued tend to have improved renal function despite a higher incidence of acute rejection. In addition, graft survival was not compromised.

Improvement in renal function also was noted in patients who underwent sirolimus-based CNI withdrawal protocols. In the Rapamune Maintenance Regimen study, 430 patients who received cyclosporine, sirolimus, and steroids were randomized at 3 months after transplantation to either remain on triple therapy or withdraw cyclosporine.[59] At 12 months, there were more acute rejection episodes in the sirolimus-steroid group: 9.8% versus 4.2% ($P = .035$). There was no difference in patient and graft survival between the 2 groups, but the calculated GFR was higher in the sirolimus-steroid group: 63 mL/min versus 57 mL/min ($P < .001$).[59] The 2-year patient and graft survival rates also were similar between the 2 groups.[60] At 36 months, the calculated GFR remained significantly better in patients who were withdrawn from cyclosporine (59.4 mL/min versus 47.3 mL/min, $P < .001$).[61] The rate of acute rejection was not significantly higher in the sirolimus-steroid group (10.2% versus 5%, $P = .171$). However, there was a trend toward better 36-month graft survival in the sirolimus-steroid group.[61]

In a subgroup of 63 patients who had protocol kidney allograft biopsies, both the mean Chronic Allograft Damage Index score and the Tubular Atrophy score were significantly lower in the sirolimus-steroid group.[62] The 4-year follow-up results of the Rapamune Maintenance Regimen study showed that patients who received sirolimus and corticosteroids had significantly better graft survival (91.5% versus 84.2%, $P = .024$) and death-censored graft survival (96.1% versus 90.6%, $P = .026$).[63] The results of this study must be interpreted with extreme caution because the control group of cyclosporine and sirolimus is known to be extremely nephrotoxic and has yielded poor results. The long-term outcomes of 3 CNI withdrawal regimens are shown in Table 1.

CNI Avoidance Regimens

In a multicenter trial, 98 kidney transplant recipients at low immunologic risk received daclizumab and steroid induction followed by maintenance immunosuppression with MMF and steroid taper.[64] CNI could be initiated after the first episode or a recurrent episode of acute rejection. The incidence of acute rejection was 48% at 6 months and 52% at 12 months.[64] The 1-year patient and graft survival was 97% and 96%, respectively. At 1 year posttransplant, 62% of patients had received CNI for more than 7 days.[64] The mean serum creatinine concentration at 1 year posttransplant was 113 μmol/L (1.28 mg/dL) (95% confidence interval, 101 μmol/L [1.14 mg/dL] to 125 μmol/L [1.42 mg/dL]) in patients who did not experience acute rejection or receive a CNI, compared with 154 μmol/L (1.75 mg/dL) (95% confidence interval, 135 μmol/L [1.53 mg/dL] to 173 μmol/L [1.97 mg/dL]) in those with acute rejection or use of CNI.[64]

Grinyó et al[65] studied the use of Thymoglobulin induction with MMF and steroid taper as maintenance immunosuppression in 30 recipients of kidneys at risk of delayed graft function (including extended criteria and non–heart beating donors). CNI was allowed if patients experienced a Banff grade II rejection or received inadequate doses of MMF. One patient had primary nonfunction and 7 patients (24%) experienced acute rejection, 6 of which were biopsy-proven.[65] The MMF dose was reduced in 28 patients and a CNI was introduced in 16 patients. Thirty-five percent of patients were receiving a CNI at 1 year posttransplant.[65] This figure increased to 64% at 5 years. The mean serum creatinine concentration was 178 μmol/L (2.0 mg/dL) and 218 μmol/L (2.5 mg/dL) at 1 and 5 years after transplantation, respectively.[65] The actuarial patient and death-censored graft survival was 94% and 83% after 1 year and 79% and 65% after 5 years, respectively.

Sixty-one kidney transplant recipients who were treated with basiliximab, MMF (2 g/d), and prednisone were randomized to receive concentration-controlled treatment with either cyclosporine or sirolimus.[66] There was no difference in the 1-year rates of acute rejection, graft survival, and patient survival between the sirolimus-treated patients (6.4%, 96.7%, and 96.7%, respectively) and the cyclosporine-treated patients (16.6%, 95.4%, and 100%, respectively). Sirolimus-treated patients also had significantly better serum creatinine concentrations at 12 months: 116 μmol/L (1.32 mg/dL) versus 157 μmol/L (1.78 mg/dL) in cyclosporine-treated patients.[67] At 2 years posttransplantation, there was no difference in the incidence of acute rejection and graft survival between the 2 groups.[67] However, renal function was better in the group that received sirolimus, with a positive slope of calculated GFR of 3.4 mL/min/y, compared with a negative slope of 1.6 mL/min/y in the cyclosporine group.[67] At 5 years, the cumulative rate of acute rejection was 12.9% versus 23.3% in the sirolimus and the cyclosporine groups, respectively.[68] Compared with cyclosporine-treated transplant recipients, sirolimus-treated patients had a higher death-censored graft survival rate of 96.4% versus 79.7% ($P = .0265$), and a higher modification of diet in renal disease (MDRD) GFR of 66.7 versus 50.7 mL/min/1.73 m^2 ($P = .0075$). However, there was no difference in patient survival: 87% versus 90%, in the sirolimus and cyclosporine groups, respectively.[68] CNI avoidance and withdrawal studies have met with mixed results. Sirolimus-based regimens tend to be poorly tolerated whereas MMF and cyclosporine regimens have prohibitive acute rejection rates.

Table 1. Long-Term Outcomes of CNI-Withdrawal Regimens in Selected Prospective, Randomized, Controlled Studies

Reference	59-61,63	58	57
Design	P, R, MC	P, R, MC	P, R, MC
Antibody induction	No	Yes except CSA(S)	NR
Maintenance regimen	SRL-based	MMF-based	MMF-based
Comparators (no. of patients)	CSA,SRL, CS (215) versus SRL, CS (215)*	CSA(S), MMF, CS (107) versus CSA(L), MMF, CS (112) versus MMF, CS (108)†	CSA, MMF, CS (77) versus MMF, CS (74)*
Acute rejection, %			
1 y	4.2 versus 9.8‡	NR	NR
2 y	5.1 versus 9.8	NR	NR
3 y	5.6 versus 10.2	27 versus 26 versus 36	NR
4 y	6.5 versus 10.2	NR	1 versus 10§
Renal function, mL/min			
1 y	53 versus 59‖¶	NR	63 versus 66#
2 y	48 versus 58‖¶	NR	NR
3 y	47 versus 59‖¶	65 versus 68 versus 67#	NR
4 y	44 versus 58‖¶	NR	NR
5 y	NR	NR	62 versus 67#**
Allograft survival, %			
1 y	96 versus 97	NR	NR
2 y	91 versus 94	NR	NR
3 y	85 versus 91††	91 versus 93 versus 85	NR
4 y	84 versus 92‡‡	NR	92 versus 88
Patient survival, %			
1 y	97 versus 98	NR	NR
2 y	93 versus 97	NR	NR
3 y	94 versus 96	93 versus 94 versus 91	NR
4 y	92 versus 95	NR	95 versus 93

Abbreviation: P, prospective; R, randomized; MC, multicenter; CSA(S), standard-dose cyclosporine; NR, not reported; SRL, sirolimus; CS, corticosteroids; CSA(L), low-dose cyclosporine.
*Cyclosporine withdrawn at 3 months.
†Cyclosporine withdrawn at 6 months.
‡$P = .035$.
§$P = .0283$.
‖Mean calculated GFR (Nankivell method).[79]
¶$P < .001$.
#Calculated creatinine clearance (Cockcroft-Gault equation).[80]
**$P = .05$.
††$P = .052$.
‡‡$P = .024$.

Other Combination Regimens

Most maintenance immunosuppressive regimens consist of a CNI, an antiproliferative agent, with or without steroids. More recently, combined use of 2 antiproliferative agents in an attempt to reduce CNI nephrotoxicity has been studied.[69] Ciancio et al[70,71] compared 3 maintenance immunosuppressive regimens in a prospective, randomized control trial. All patients received daclizumab induction. In addition to maintenance steroids, 50 patients received tacrolimus and sirolimus, 49 received tacrolimus and MMF, and 48 received cyclosporine microemulsion and sirolimus[70,71]: the incidence of acute rejection at 1 year was 4%, 4%, and 14%, respectively ($P = .03$),[70] and there was no dif-

ference in the mean creatinine clearance among the groups: 73 versus 84 versus 71 mL/min, respectively.[71] However, the average creatinine clearance of patients receiving sirolimus and a CNI (tacrolimus or cyclosporine) was significantly lower compared with those receiving tacrolimus and MMF. There was no difference in 1-year graft survival: 100%, 98%, and 96%, in the tacrolimus/sirolimus, tacrolimus/MMF, and the cyclosporine microemulsion/sirolimus treated patients, respectively.[71]

The Prograf Study group conducted a multicenter, prospective, randomized trial comparing sirolimus with MMF in a tacrolimus-based maintenance regimen.[72] In addition to tacrolimus and steroids, 185 patients received sirolimus and 176 received MMF. Only patients with delayed graft function received antibody induction.[72] The rate of acute rejection at 6 months was not different between sirolimus- and MMF-treated patients: 13% versus 11.4%, respectively. However, MMF patients had a lower median serum creatinine concentration at 6 months with 127 μmol/L (1.44 mg/dL) versus 156 μmol/L (1.77 mg/dL)[72] and at 1 year with 114 μmol/L (1.3 mg/dL) versus 132 μmol/L (1.5 mg/dL), respectively.[73] The mean creatinine clearance at 1 year was lower in sirolimus-treated patients (54.3 versus 58.4 mL/min, $P = .06$).[73] There was no difference in 1-year graft survival between sirolimus- and MMF-treated patients: 90.8% versus 94.3%, respectively.[73] There was more discontinuation of sirolimus as a result of adverse effects in sirolimus-treated patients than MMF in MMF-treated patients at the 1 year follow-up evaluation: 20.4% versus 11%, respectively.[73]

In a 6-month, multicenter, randomized study of 977 kidney transplant recipients, Vitko et al[74] compared the efficacy of the combined regimens of tacrolimus with 1 of 2 different doses of sirolimus: 2 mg/d or 0.5 mg/d with a regimen of tacrolimus and MMF of 1 g/d. Steroids were administered to all groups. The incidence of biopsy-proven acute rejection was 15.7% in the tacrolimus-sirolimus 2-mg group compared with the tacrolimus-sirolimus 0.5-mg group 25.2% ($P = .003$) and the tacrolimus-MMF group 22.3% ($P = .036$).[74] The 6-month graft survival was 91.0%, 92.6%, and 92.4% in the tacrolimus-sirolimus 2-mg, tacrolimus-sirolimus 0.5-mg, and the tacrolimus-MMF groups, respectively. The respective patient survival rate was 98.1%, 97.8%, and 97.9%.[74]

Gallon et al[75] reported a pilot, open-label, prospective study of 82 kidney transplant recipients of low immunologic risk randomized to 2 steroid-free maintenance regimens that consisted of either tacrolimus and sirolimus or tacrolimus and MMF. All patients received IL-2–receptor antibody induction. The incidence of acute rejection was not significantly different: 29.7% (sirolimus group) versus 17.7% (MMF group).[75] Renal function (MDRD GFR) was significantly lower in the sirolimus group throughout the 3-year study period. The mean slope of GFR change was −0.38 mL/min/1.73 m^2/mo (sirolimus group) versus 0.069 mL/min/1.73 m^2/mo (MMF group) ($P = .07$).[75] The Kaplan-Meier allograft survival at 3 years was lower in the sirolimus group: 84% versus 98% ($P = .04$). There was no difference in the 3-year patient survival.[75]

Larson et al[76] compared the efficacy of sirolimus versus tacrolimus in an MMF-based regimen in a single-center, open-label, prospective trial. A total of 165 patients, predominantly Caucasian live-donor kidney recipients, were randomized to receive either a regimen of tacrolimus, MMF, and prednisone, or sirolimus, MMF, and prednisone. All patients received Thymoglobulin induction.[76] There was no difference in the rate of acute rejection between the 2 groups: 14% versus 19%, respectively. The 1-year patient survival rate was 96% versus 98%, respectively, and the 1-year death-censored graft survival was 96% in both groups.[76] Although renal function measured by iothalamate GFR was not different between the 2 groups: 55 mL/min/1.73 m^2 versus 56 mL/min/1.73 m^2 at 1 year and 55 mL/min/1.73 m^2 at 2 years in both groups, patients who received sirolimus had a significant decline in GFR between 1 month and 1 year posttransplantation from 62 mL/min/1.73 m^2 to 56 mL/min/1.73 m^2. There were more patients in the tacrolimus group with chronic vascular changes on protocol kidney allograft biopsies but there was no difference in the proportion of patients with tubular atrophy and interstitial fibrosis.[76] Importantly, 38% of the sirolimus patients discontinued sirolimus be-

Table 2. Short-Term Outcomes of CNI- and MMF-Based Combination Regimens in Selected Prospective, Randomized, Controlled Studies

Reference	70,71	72,73	76	77
Design	P, R, SC	P, R, MC	P, R, SC	P, R, MC
Antibody induction	Yes	Yes if DGF	Yes	Yes
Maintenance regimen	CNI based	TAC based	MMF based	MMF based
Comparators (no. of patients)	TAC, MMF, CS (50) versus TAC, SRL, CS (50) versus CSA, SRL, CS (50)	TAC, MMF, CS (176) versus TAC, SRL, CS (185)	TAC, MMF, CS (84) versus SRL, MMF, CS (81)	TAC, MMF, CS (402) versus SRL, MMF, CS (399) versus CSA^L, MMF, CS (399) versus CSA^N, MMF, CS (385)
Acute rejection at 1 year, %	4 versus 4 versus 14*	11 versus 13 (6 mo)	14 versus 19	12 versus 35 versus 24 versus 25‡
Renal function, mL/min†	84 versus 73 versus 71§	58 versus 54‖	55 versus 56¶	65 versus 56 versus 59 versus 56‡
Allograft survival, %	90 versus 96 versus 92	94 versus 91	92 versus 94	94 versus 89 versus 93 versus 90#
Patient survival, %	92 versus 96 versus 98	97 versus 96	96 versus 98	97 versus 97 versus 98 versus 97
Discontinuation or cross-over rate, %	8 versus 38 versus 57**	15 versus 27††	16 versus 38‡‡	NR

Abbreviation: P, prospective; R, randomized; SC, single center; MC, multicenter; DGF, delayed graft function; TAC, tacrolimus; CS, corticosteroids; SRL, sirolimus; CSA^L, low-dose cyclosporine; CSA^N, normal-dose cyclosporine; NR, not reported.
*$P = .03$, combined TAC-MMF and TAC-SRL groups versus CSA-SRL group.
†Mean creatinine clearance (Cockcroft-Gault equation) except where indicated.
‡$P < .01$, TAC versus all other groups.
§$P = .05$, TAC-MMF versus CSA-SRL.
‖$P = .06$, median creatinine clearance.
¶Mean iothalamate clearance (mL/min/1.73 m^2).
#$P < .05$, TAC versus SRL and CSA^N.
**$P = .00001$, comparison among the 3 groups.
††$P = .006$.
‡‡P value not reported.

cause of adverse effects, compared with 17% of tacrolimus patients.[76]

The SYMPHONY trial compared standard immunosuppression that consisted of conventional doses of cyclosporine (trough level, 150-300 ng/mL for 3 months and 100-200 ng/mL thereafter), MMF 1 g twice daily, and steroids (n = 385) with each of 3 regimens that included daclizumab induction, MMF 1 g twice daily, and steroids, and either low-dose cyclosporine (trough level, 50-100 ng/mL) (n = 399), low-dose tacrolimus (trough level, 3-7 ng/mL) (n = 402), and low-dose sirolimus (trough level, 4-8 ng/mL) (n = 399).[77] The mean 12-month GFR was significantly higher with the low-dose tacrolimus regimen (64.5 mL/min) compared with conventional-dose cyclosporine (56.2 mL/min), low-dose cyclosporine (58.9 mL/min), and low-dose sirolimus regimens (55.9 mL/min). The incidence of biopsy-proven acute rejection at 12 months was also significantly lower with the low-dose tacrolimus regimen (12.3%) compared with conventional-dose cyclosporine (25.3%), low-dose cyclosporine (23.5%), and low-dose sirolimus regimens (35.3%). The respective 12-month allograft survival was 94.2%, 90%, 93.1%, and 89.2%.[77] The recently completed CAESAR study found that low-dose cyclosporine

Table 3. Long-Term Outcomes of CNI- and MMF-Based Combination Regimens in Selected Prospective, Randomized, Controlled Studies

Reference	25-27	66-68	75
Design	P, R, MC	P, R, SC	P, R, MC
Antibody induction	Yes if DGF	Yes	Yes
Maintenance regimen	CNI based	MMF based	CNI based
Comparators (no. of patients)	TAC, MMF, CS (72) versus TAC, AZA, CS (76) versus CSA, MMF, CS (75)	SRL, MMF, CS (31) versus CSA, MMF, CS (30)	TAC, MMF (45) versus TAC, SRL (37)
Acute rejection, %			
1 y	15 versus 17 versus 20	6.4 versus 16.6	NR
2 y	17 versus 18 versus 23	6.5 versus 16.6	NR
3 y	17 versus 21 versus 25	NR	18 versus 30
5 y	NR	12.9 versus 23.3	NR
Renal function			
1 y	61 versus 63 versus 55*	81 versus 61†‡	64 versus 50§‖
2 y	NR	80 versus 63†‡	61 versus 47§¶
3 y	59 versus 62 versus 56*	NR	62 versus 42§**
5 y	NR	67 versus 51§††	NR
Allograft survival, %			
1 y	89 versus 88 versus 87	97 versus 95	NR
2 y	83 versus 84 versus 77	94 versus 93	NR
3 y	81 versus 80 versus 73‡‡	NR	98 versus 84§§
5 y	NR	84 versus 77‖‖	NR
Patient survival, %			
1 y	93 versus 96 versus 89	97 versus 100	NR
2 y	94 versus 96 versus 88	94 versus 100	NR
3 y	NR	NR	100 versus 98
5 y	NR	87 versus 90	NR

Abbreviation: P, prospective; R, randomized; MC, multicenter; SC, single center; DGF, delayed graft function; TAC, tacrolimus; CS, corticosteroids; AZA, azathioprine; NR, not reported.
*Median creatinine clearance (Cockcroft-Gault equation) in mL/min.
†Mean creatinine clearance (Cockcroft-Gault equation) in mL/min.
‡$P = .008$.
§Mean glomerular filtration rate (abbreviated Modification of Diet in Renal Disease [MDRD] equation) in mL/min/1.73 m^2.[81]
‖$P = .0024$.
¶$P = .0008$.
**$P = .0001$.
††$P = .0075$.
‡‡TAC/MMF/CS versus CSA/MMF/CS 84% versus 50%, $P = .02$ in patients with DGF.
§§$P = .04$.
‖‖Death-censored graft survival SRL versus CSA, 96% versus 80%, $P = .0265$.

in combination with MMF and corticosteroids showed equivalent acute rejection rates to a higher dose cyclosporine regimen and 10% less acute rejection and equivalent renal function to a cyclosporine-withdrawal group.[78]

The short-term and long-term outcomes of different combination regimens are shown in Tables 2 and 3, respectively.

CONCLUSIONS

Introduction of the IL-2–receptor antibodies, tacrolimus, MMF, and sirolimus, has facilitated the development of steroid- and CNI-sparing regimens. Early steroid withdrawal appears successful in patients with low-normal immunologic risks, but up to 30% of patients eventually

may require steroids. Although the combination of MMF with CNIs decreases acute rejection episodes and is well tolerated, the use of sirolimus with either cyclosporine or tacrolimus has been associated with increased nephrotoxicity and worse graft survival. In general, avoidance of CNIs results in better short-term renal function but a higher incidence of acute rejection. The impact of CNI-free regimens, such as the sirolimus/MMF combination, on long-term graft survival requires further studies. The antilymphocyte agent Thymoglobulin is associated with lower acute rejection rates than the IL-2–receptor antibodies, but no difference in graft survival has been noted.

Recent large-scale studies such as the SYMPHONY and CAESAR studies seem to indicate that for the time being regimens using low-dose CNIs along with MMF may achieve the best balance between renal function and prevention of acute rejection. The long-term outcomes with total CNI avoidance and withdrawal still require longer follow-up evaluation, particularly with the newer agents such as Belatacept.

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