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Immunosuppression for Long-Term Maintenance of Renal Allograft Function

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Contents

Abstract

The incidence and severity of acute rejection episodes was markedly reduced by the introduction of new immunosuppressive drug regimens for renal transplantation, resulting in improved graft survival at 1 year. However, only modest improvement has been shown in long-term graft function rates.

This overview evaluates the efficacy of currently used immunosuppressive drugs and drug combinations for long-term maintenance therapy. Prospective controlled trials rarely extend beyond 5 years; therefore, registry data and retrospective reports have also been employed. From currently available data it may be concluded that the initial beneficial effect of ciclosporin (cyclosporin) is lost 10 years after transplantation. Tacrolimus is an alternative to ciclosporin with a different profile of adverse effects and a higher efficacy in acute rejection treatment. For long-term maintenance, projected half-lives of kidney graft function are in favour of tacrolimus. Mycophenolate mofetil (MMF) has been shown

to significantly reduce the incidence of early rejections. However, the improved long-term graft survival reported in retrospective studies has still to be confirmed in controlled trials. There is no convincing evidence for superiority of triple therapy including prednisone (or prednisolone), calcineurin inhibitors and azathioprine/MMF over dual therapy without azathioprine/MMF with respect to long-term outcome. Withdrawal of corticosteroids or calcineurin inhibitors clearly reduces adverse drug effects but carries the risk of acute rejection episodes. Avoidance of corticosteroids by using new immunosuppressive drug combinations may be an option to minimise toxic adverse effects in the future.

At present, it seems unjustified to convert renal transplant recipients with stable graft function and tolerable adverse effects from one drug to another solely in expectation of future benefits. Acute early or late rejection episodes and intolerable adverse effects are good reasons for conversions between calcineurin inhibitors or cytotoxic agents. Chronic allograft nephropathy with slowly deteriorating graft function remains an unresolved problem.

Introduction of the calcineurin inhibitors, ciclosporin (cyclosporin) and tacrolimus, has resulted in considerable improvements in short-term renal graft survival over the last two decades. However, only a modest improvement has been shown in long-term graft function rates. Chronic allograft nephropathy and recipient mortality are the two major factors contributing to a continuous loss of functioning kidney grafts after the first year of transplantation.

Chronic renal graft dysfunction results from immunological injury in the form of chronic allograft rejection as well as from non-immunological vascular risk factors such as hypertension, hyperlipidaemia or post-transplant diabetes mellitus. Recipient mortality beyond the first year of transplantation is mainly because of cardiovascular events, malignancy and infection.

1. Death with Graft Function

Death with graft function is a common cause of graft loss. In a population-based survival analysis of 86 502 adult patients transplanted between 1987 and 1998,[1] 38% of the 18 482 deaths were deaths with graft function, accounting for 42.5% of all graft loss. The predominant cause of death with graft function was cardiovascular disease (36.1%). Immunosuppressive agents aim to avoid the immunological injury to the graft, but most of these drugs simultaneously increase non-immunological risk factors, rate of malignancies and risk of systemic infection to some degree and in this way contribute to chronic allograft dysfunction and recipient mortality. Thus, the effect of a specific immunosuppressive drug on long-term outcome after kidney transplantation is rather complex. In addition, immunosuppressive regimens after transplantation usually consist of combinations of two or three drugs that change over time; drugs being substituted, added or withdrawn. The impact of immunosuppressive regimens on cardiovascular risk factors (hypertension, hyperlipidaemia, diabetes) has been described previously.[2-4] However, it still has to be demonstrated that different risk profiles or control of risk factors translate into the expected improvement of graft and patient survival.

2. Surrogate Endpoints Predicting Long-Term Graft Survival

In order to avoid the difficulties of performing and completing long-term clinical studies on immunosuppression, short-term parameters have been looked for to predict the outcomes after renal transplantation. Delayed graft function and acute rejection during the first year have a significant adverse effect on long-term graft survival.[5] Renal function, especially serum creatinine level or calculated glomerular filtration rate (GFR) at 1 year post-transplant, has been proposed as a predictor of long-term

graft survival.[6-8] However, retrospective evaluation of a large set of transplant data from the US Renal Data System found a limited utility of renal function as a predictive tool for graft loss.[9] Protocol graft biopsies at 6 months[10] or 1 year[11] are a more invasive approach to predict late outcome. So far, predictors of outcome have only been analysed retrospectively and will need confirmation in a prospective fashion.

3. Methods of Literature Search and Evaluation

There is no definition of 'long-term' function after kidney transplantation. In the literature, the term is used for any time period between 2 years and more than 10 years. This overview regards observations as 'long term' if they cover 5 years or longer. Randomised, controlled studies on immunosuppressive drug effects are rarely designed for such a long time. At best, patients originally entered into a study have been re-evaluated outside the protocol at a later time. Most long-term data available in the literature are merely descriptive, retrospective, non-randomised and uncontrolled. In addition, registry data have been published, and these have the advantage of large numbers and, sometimes, long observation times. However, with respect to immunosuppressive regimens, a selection bias is often unknown or difficult to detect.

This overview attempts to compare the long-term results of immunosuppressive regimens, mainly on an intention-to-treat basis using published data mostly from controlled trials, but also uncontrolled single-centre reports and retrospective data from registries. The literature search was performed with PubMed, using immunosuppressive drug names and 'renal transplantation' as primary search terms. The search focussed on studies published between 1998 and 2003 reporting follow-up data beyond 5 years.

4. Immunosuppressive Drugs for Renal Transplantation

Immunosuppressive drugs used in kidney transplantation can be grouped according to their mechanism of action.

4.1 Corticosteroids

Glucocorticoids[12] were the first and, intially, the only drugs used for kidney transplantation. Prednisone (or prednisolone) is the most commonly given compound to prevent or treat graft rejection. Since prednisone still has most of the mineralocorticoid efficacy of the natural cortisol, some centres prefer the more expensive but less sodium-retaining methylprednisolone for high-dosage intravenous application. Corticosteroids exert their unique combination of antiproliferative, anti-inflammatory and immunosuppressive effects via binding to a cytosolic glucocorticoid receptor expressing or suppressing a number of genes regulating, among others, phospholipase A2 and some interleukins (IL). Only recently have attempts been undertaken on a larger scale to transplant solid organs without any corticosteroids.[13]

4.2 Cytotoxic Agents

Lymphocytes have no 'salvage pathway' for purine production and, therefore, depend on *de novo* purine synthesis for proliferation. Azathioprine[14] was the second drug to be introduced into renal transplantation. The prodrug azathioprine is cleaved to the purine analogue mercaptopurine in the body and inhibits RNA and DNA synthesis. Mycophenolic acid[15] blocks inosine-monophospate-dehydrogenase activity and, in this way, inhibits *de novo* purine synthesis. The prodrug mycophenolate mofetil (MMF) reached the market in the second half of the 1990s. Mofetil improves drug bioavailability and is cleaved from the mycophenolic acid after intestinal absorption. Very recently an enteric-coated formulation of MMF has become available.

4.3 Calcineurin Inhibitors

Calcineurin inhibitors mainly decrease the synthesis of IL-2 in activated T cells. Ciclosporin[16,17] binds to cyclophilins in the T cell, inhibits the calcineurin-calmodulin complex and impairs IL-2 gene expression. Ciclosporin A came into use in transplant medicine during the early 1980s. It is usually referred to as 'ciclosporin', although other

ciclosporins (i.e. ciclosporin G) have been tested clinically. Over the years, different formulations of ciclosporin have been used. The data evaluated in this overview have nearly all been obtained with ciclosporin microemulsion, which has been shown to have a more reliable bioavailability than older formulations, leading to more efficient immunosuppression and reduced incidence of acute rejection episodes.[18,19] Tacrolimus[20] was marketed about 10 years later. After binding to other intracellular proteins (FK-binding protein), tacrolimus exerts the same mechanism of action as ciclosporin. On a weight basis it is more active than ciclosporin and differs in some drug adverse effects.

4.4 Inhibitors of Interleukin-2 Receptor Signal Transduction

Sirolimus (rapamycin)[21] blocks signal transduction from the activated IL-2 receptor and, in this way, inhibits T-cell proliferation. It came into larger scale use for organ transplantation only around the year 2000. Therefore, long-term results from sirolimus-treated recipients are still not available and are only briefly discussed in this overview.

4.5 Antilymphocytic Antibodies

Antibodies[22-25] directed against T cells (antithymocyte globulin), the T-cell receptor (anti-CD3 antibodies) or the IL-2 receptor (anti-CD25 antibodies) are used for induction therapy at the time of transplantation or for treatment of severe rejection episodes. Long-term results of renal transplantation are only indirectly influenced by their use.

5. Immunosuppressive Drug Combinations for Renal Transplantation

With the introduction of new drugs, immunosuppressive maintenance regimens after kidney transplantation have changed over time. Table I provides an overview of the most commonly used drug combinations. Prednisone plus azathioprine was the only drug combination available until the early 1980s. Substitution of azathioprine by ciclosporin improved 1-year graft survival by about 20%. Multicentre trials showed the superiority of ciclosporin over azathioprine at 3[26] and 5[27] years. When triple therapy came into use towards the end of the 1980s, azathioprine was reintroduced into standard maintenance protocols and substituted by mycophenolic acid about 10 years later. The calcineurin inhibitor tacrolimus became an alternative to ciclosporin during the early 1990s. Registry data[28,29] and single-centre reports[30] show improved graft and recipient survival over these years, which may in part reflect the effects of the new immunosuppressive regimens. However, whether this is only explained by the remarkable improvement in short-term graft survival or also by an increase in the half-life of graft function is yet to be resolved.[31,32]

Table I. Most commonly used immunosuppressive drug combinations for maintenance therapy in renal transplantation

Time period[a]	Preferred regimen(s)
Pre 1982	P-AZA
1983–9	P-CSA
1990–6	P-CSA-AZA
	P-TAC-AZA
Post 1996	P-CSA-MMF
	P-TAC-MMF

a Time periods are estimates and differ according to regional drug approval and centre preferences.

AZA = azathioprine; **CSA** = ciclosporin; **MMF** = mycophenolate mofetil; **P** = prednisone (or prednisolone); **TAC** = tacrolimus.

5.1 Ciclosporin-Based Regimens

Most centres reported that the introduction of ciclosporin resulted in a significantly better short-term graft survival. Improved graft survival rates were maintained at 10-year follow up in some studies,[33,34] but lost in the long term in other trials.[35,36] In a prospective, randomised study[37] comparing ciclosporin plus azathioprine plus prednisone (n = 58) with azathioprine plus prednisone (n = 59) in low-risk recipients, 12-year graft survival in the ciclosporin arm (59%) was not significantly better than in the patients who did not receive ciclosporin (56%) and the ciclosporin group had poorer renal function.

A meta-analysis[38] of seven controlled trials showed no significant advantage of triple ciclosporin-azathioprine-prednisone therapy over

dual ciclosporin-prednisone in terms of graft survival. In a randomised study comparing ciclosporin monotherapy with dual ciclosporin-prednisone and triple ciclosporin-azathioprine-prednisone therapy in 354 recipients with a median follow up of 85 months, graft survival was not significantly different between the study groups at 9 years.[39] Nearly one-half of the patients in the monotherapy arm had received corticosteroids during the course of the study. Registry data covering the years 1991 through 2000 also revealed a short-term improvement in graft survival on triple therapy, but the addition of azathioprine did not affect the graft half-lives.[40]

In a case control study in 102 patients, younger renal transplant recipients and those with highly variable ciclosporin exposure were at risk of developing chronic allograft nephropathy.[41] C2 ciclosporin monitoring has been advocated for better control of ciclosporin exposure in the early phase after transplantation. For long-term ciclosporin monitoring, no convincing advantage of C2 monitoring over measuring trough concentrations could be demonstrated in 161 patients after the first year of kidney transplantation.[42]

The introduction of ciclosporin certainly had a major beneficial impact on early results of kidney transplantation. However, obviously, the drug is less effective in late renal graft maintenance and addition of azathioprine does not improve long-term results in a substantial manner.

5.2 Tacrolimus-Based Regimens

Tacrolimus was introduced for use in kidney transplantation at a time when triple therapy was more or less used as standard maintenance immunosuppression. The short- and middle-term efficacy of triple tacrolimus-azathioprine-prednisone therapy has been compared with dual tacrolimus-prednisone therapy in randomised trials. The Pittsburgh Transplantation Institute[43] and, more recently, a European study group[44] did not find any differences in over 200 patients in each study between both treatment arms in graft or patient survival, or number or type of rejection episodes at 1 year. The Spanish and Italian Tacrolimus Study Group reported results at 1, 2 and 3 years in 475 recipients.[45-47] At each time point, graft and patient survival was virtually identical with dual tacrolimus-prednisone or with triple tacrolimus-azathioprine-prednisone therapy.

Although the observation periods of these ongoing studies are shorter than 5 years, it is unlikely from the results obtained so far that an additional long-term effect of azathioprine in combination with tacrolimus will evolve in the following years.

5.3 Ciclosporin versus Tacrolimus

Initial randomised, short-term studies did not find any significant difference between ciclosporin- and tacrolimus-based regimens in patient or graft survival at 1[48] or 3[49] years after transplantation. In an analysis of more than 32 000 renal graft recipients both ciclosporin microemulsion and tacrolimus were associated with significantly lower risk of chronic allograft failure than conventional ciclosporin formulation at 4 years. The results with ciclosporin microemulsion and tacrolimus were similar.[50]

Protocol biopsies at 1 year after transplantation were performed in a randomised study (n = 102) comparing ciclosporin and tacrolimus.[51] Despite equivalent risk factors for chronic allograft nephropathy before transplantation and short-term efficacy after grafting, the use of ciclosporin was associated with increased allograft fibrosis compared with tacrolimus. In a single-centre, retrospective evaluation of 5 years' experience in 217 transplanted patients, those treated with tacrolimus had fewer rejection episodes and a better graft survival than patients treated with ciclosporin microemulsion.[52]

Six-year follow-up data from 232 recipients randomised to treatment with tacrolimus or ciclosporin in a single centre were analysed.[53] Morphometric evaluation of protocol biopsies performed at 1 year revealed that the degree of interstitial fibrosis was significantly greater in the ciclosporin group. Patients receiving tacrolimus had significantly better 6-year graft survival and a longer projected

half-life of 15 years versus 10 years with ciclosporin.

Two major multicentre trials comparing tacrolimus- and ciclosporin-based immunosuppressive therapy reported 5-year results. Intent-to-treat analysis of the US multicentre trial revealed equivalent patient and graft survival between treatment arms.[54] The rate of crossover to the tacrolimus treatment arm was significantly higher among the patients randomised to ciclosporin-based therapy. Only when crossover for rejection was regarded as graft failure was 5-year graft survival significantly better with tacrolimus (64%) than with ciclosporin (54%). In the European study, including 451 transplant patients, graft survival rates at 5 years post-transplant were 68% in the tacrolimus and 66% in the ciclosporin groups; patient survival rates were also comparable.[55] With tacrolimus, the number of chronic rejections was significantly lower and the projected half-life was also in favour of tacrolimus (15.8 vs 10.8 years).

In 986 paediatric recipients, tacrolimus and ciclosporin in combination with MMF and corticosteroids, produced similar rejection rates and graft survival at 1 and 2 years.[56] Tacrolimus was associated with better graft function at both timepoints. It remains to be determined whether the difference in graft function translates into improved long-term graft survival.

The middle- or long-term studies comparing ciclosporin and tacrolimus for primary immunosuppression after kidney transplantation nearly all confirm earlier reports on differences in the safety profile between both drugs. Patients receiving primary therapy with tacrolimus,[57] and those converted from ciclosporin to tacrolimus,[58,59] had a more favourable lipoprotein pattern with lower cholesterol, low-density lipoproteins and apolipoprotein B. In addition, blood pressure decreased after conversion to tacrolimus.[60,61] Gingival hyperplasia and hirsutism, adverse effects of ciclosporin, showed rapid improvement in all patients experiencing these effects and had disappeared after 1 year of tacrolimus therapy.[62] Neurotoxicity, disturbances in glucose metabolism and gastrointestinal symptoms are more pronounced or more frequent with tacrolimus.[48] In a cohort of 139 renal graft recipients without known glucose metabolism abnormalities who were treated with tacrolimus, 15% developed impaired fasting glycaemia and 32% developed diabetes in the first year after transplantation.[63] In addition, tacrolimus has been associated with polyomavirus disease as a cause of renal graft dysfunction or renal graft loss.[64] In all of the conversion studies, the switch from ciclosporin- to tacrolimus-based maintenance immunosuppression proved to be a safe procedure and renal graft function remained stable. Finally, a cost analysis from Italy found an advantage for tacrolimus in direct medical costs.[65]

The pros and cons of tacrolimus versus ciclosporin have been recently reviewed by Scott et al.[66] and Tanabe.[67] Well tolerated and effective immunosuppression is feasible with either ciclosporin or tacrolimus. However, the different profile of adverse effects might influence the decision for one or the other substance in an individual patient. For long-term maintenance, projected half-lives of kidney graft function are in favour of tacrolimus. The superior effect of tacrolimus in the treatment of acute rejection has also been reviewed.[68] Especially with regards to the control of vascular acute rejection, a better potential long-term outcome is hoped for with tacrolimus, and a number of centres routinely convert patients from ciclosporin to tacrolimus for acute rejection. In a prospective controlled study,[69] 119 recipients were switched to tacrolimus or maintained on ciclosporin at a first episode of biopsy-proven acute rejection. Tacrolimus reduced the number of corticosteroid-resistant rejections and the risk of recurrent rejection; short-term graft survival was similar in both groups.

At present, there is some hope for a long-term beneficial effect of tacrolimus in kidney transplantation but no hard evidence exists. However, early conversion from ciclosporin to tacrolimus in the case of rejection episodes or adverse effects appears to be a wise choice.

5.4 Azathioprine versus Mycophenolate Mofetil

Before registration of MMF, three large controlled, multicentre trials were performed comparing MMF with placebo[70] or azathioprine[71,72] in ciclosporin-based regimens for cadaveric kidney transplantation. At 1 year, MMF reduced the incidence of acute rejection significantly in each study but did not significantly improve graft or patient survival. Three-year follow-up reports have been published from all three studies, evaluating the original study population in an intention-to-treat fashion.[73-75] Despite the reduction of rejection episodes during the first 6 months, graft and patient survival at 3 years were similar to the results achieved with azathioprine. The European Mycophenolate Mofetil Cooperative Study Group[73] reported a reduction in the incidence of graft loss by 7.6% with MMF compared with placebo. Gastrointestinal toxicity, invasive cytomegalovirus infection and fungal infections were seen more frequently with MMF than with placebo, especially when higher dosages of 3 g/day were used.

The long-term continuous use of MMF versus azathioprine was associated with a protective effect against declining renal function at 1 and 2 years when a large number of transplantations was analysed from the US Renal Data System.[76] In a 3-year analysis, patient survival and death-censored graft survival were significantly improved in MMF-treated compared with azathioprine-treated high-risk African American graft recipients. The benefit was comparable with the benefit achieved with MMF over azathioprine in Caucasian patients.[77] The relative risk of developing chronic allograft failure was also analysed at 4 years post-transplant from registry data.[78] MMF significantly reduced the risk by 27% compared with azathioprine. This effect could only partly be explained by the reduced incidence of acute rejection episodes in the early phase after transplantation.

Five-year outcome comparing ciclosporin-based immunosuppression with azathioprine or MMF has been reported in a retrospective analysis of single-centre data.[79] In 308 recipients a nonsignificant trend towards better graft survival with MMF was evident at 2 years and persisted at 5 years. Extrapolation of half-lives indicated that about 10% more kidney grafts would still be functioning on combination therapy with MMF versus azathioprine. In a prospective single-centre experience[80] with 38 patients in each group receiving either MMF or azathioprine as part of a triple-drug regimen including ciclosporin, uncensored graft and patient survival showed a similar tendency for improved results with MMF at 1, 3 and 5 years, but the differences did not reach statistical significance.

A subgroup of 73 patients from a larger trial using tacrolimus-MMF-prednisone was analysed at 4 years.[81] The authors concluded that MMF reduced the incidence of acute rejection episodes in tacrolimus-treated patients during the initial period after transplantation but could be safely withdrawn. At 4 years there were no significant differences in graft or patient survival between patients receiving tacrolimus-MMF-prednisone and tacrolimus-prednisone. Data on the combination of azathioprine or MMF with tacrolimus can also be obtained from a three-arm multicentre study[82] investigating tacrolimus with azathioprine or MMF versus ciclosporin with MMF in 223 patients. At 1 year there were no significant differences in overall graft or patient survival between groups. The incidence of corticosteroid-resistant rejections was substantially lower in the tacrolimus plus MMF group, and the incidence of post-transplant diabetes was highest in the tacrolimus plus azathioprine group. Three-year data from the same study in principle corroborate these findings.[83] The subgroup of recipients with delayed graft function in the tacrolimus plus MMF arm had improved graft survival compared with the other two groups.

In the initial studies on MMF combinations it was disappointing to find that, despite a significant reduction in the incidence of acute rejection episodes, graft survival was not improved as expected. Five-year results and analysis of registry data at least suggest that MMF might have more potential than azathioprine to improve kidney graft outcome in the long term.

5.5 Reduction, Withdrawal or Avoidance of Calcineurin Inhibitors

A number of centres reduce the dose of calcineurin inhibitors during the late phase after transplantation. In a prospective, randomised trial in 64 stable renal graft recipients, a 50% ciclosporin dose reduction ≥1 years after transplantation was not associated with an increased risk of rejection within 6 months as observed in ciclosporin withdrawal studies.[84] Protocol biopsies revealed no adverse effects of ciclosporin reduction over 3 years.[85] On the other hand, analysis of kidney transplant data from the Collaborative Transplant Study database[86] showed that the 1-year ciclosporin dose was significantly associated with long-term graft survival. Patients receiving 3–6 mg/kg/day 1 year after transplantation had the best graft survival rate at 10 years, whereas treatment with <3 mg/kg/day carried the risk of under-immunosuppression.

In a meta-analysis of immunosuppression withdrawal trials, ciclosporin withdrawal was associated with a significant risk of acute rejection but did not increase the risk of graft failure.[87] In a controlled trial, conversion from ciclosporin to azathioprine treatment 1 year after transplantation in 216 recipients resulted in improved renal function and better blood pressure control at 5 years and no significant difference in 10-year graft and patient survival.[88] Early ciclosporin withdrawal in 252 live related renal transplantations involved a considerable risk of acute rejection and subsequent chronic rejection, whereas withdrawal beyond the first year appeared to be better tolerated in stable recipients.[89] In a single-centre study, 128 patients receiving ciclosporin and prednisone were randomised to continue ciclosporin treatment or to be converted from ciclosporin to azathioprine 3 months after transplantation.[90] Fifteen years after transplantation graft survival tended to be lower in the ciclosporin continuation group and GFR was significantly higher in the patients converted to azathioprine.

Ciclosporin withdrawal in MMF-treated kidney graft recipients has been investigated in prospective, controlled, multicentre trials from The Netherlands and Belgium. In 212 patients receiving triple-drug therapy including MMF, withdrawal of ciclosporin resulted in a significantly increased incidence of biopsy-proven acute and chronic rejection.[91] However, at 2 years graft and patient survival were not different between groups. In another similar study with 187 patients enrolled from 21 centres, a modest increase in acute rejections without graft loss was observed in those patients who had ciclosporin withdrawn.[92]

Reduced-dose tacrolimus (trough concentrations of 5–10 μg/L) after anti-CD25 antibody induction has been investigated in a single-centre study.[93] Tacrolimus was part of a triple-drug regimen with MMF and corticosteroids in 82 recipients. Compared with normal-dose tacrolimus (trough concentrations of 10–15 μg/L) without induction, the short-term results indicated a better graft survival with the reduced-dose regimen. For sirolimus, which is also being used for calcineurin inhibitor reduction or withdrawal, at present only short-term observations are available.[94,95]

Avoidance of calcineurin inhibitors employing new immunosuppressive drugs has been discussed.[96] Regimens using IL-2-receptor antibody induction and MMF plus corticosteroids experienced high rates of early rejection episodes[97,98] and no long-term data are available. At present the role of sirolimus or of new antibodies, such as anti-CD52, aiming at graft tolerance in the prevention of chronic graft nephropathy without calcineurin inhibitors cannot be assessed because no long-term data are available.

5.6 Withdrawal or Avoidance of Corticosteroids

Because of their well-known toxic adverse effects, the dosage of corticosteroids was reduced as part of immunosuppressive drug therapy after renal transplantation in almost all centres when calcineurin inhibitors became available. Soon after the introduction of ciclosporin, attempts at complete withdrawal of corticosteroids were made.[99,100] Although the rate of early rejection episodes seemed acceptable when patients were converted from corticosteroids to azathioprine, re-evaluation after 8

years showed that in a high percentage of patients corticosteroids had been reinstituted because of biopsy-proven chronic rejection.[101] Meta-analysis of nine controlled corticosteroid withdrawal trials found that the relative risk for acute rejection or for graft failure was increased 1.4-fold.[87] Despite an improved adverse effect profile in corticosteroid-free patients (compared with those patients receiving corticosteroids), with significantly less frequent cataracts, osteoporosis and cardiovascular complications,[39] the long-term safety and efficacy of this approach has been questioned.[102]

Favourable 4-year experience with corticosteroid withdrawal was reported in 19 children receiving tacrolimus-based immunosuppression.[103] As with calcineurin inhibitors, the long-term feasibility of corticosteroid withdrawal from drug regimens with newer immunosuppressants is hoped for, but cannot be assessed yet.

Complete avoidance of corticosteroids is an approach favoured in the early 2000s and has been recently reviewed.[13] The rationale behind this approach is to avoid a probably IL-mediated effect of corticosteroid withdrawal in patients conditioned to corticosteroid treatment for a certain period of time. Combinations of modern immunosuppressive drugs seem to allow corticosteroid-free transplantation[104] and, thus, to bypass withdrawal effects. With respect to long-term outcome, these observations are certainly preliminary but provide an encouraging outlook.

5.7 Immunosuppressive Regimens with Sirolimus

In contrast to calcineurin inhibitors, sirolimus does not impair renal GFR. It has been successfully used in calcineurin inhibitor-free protocols with antibody induction in recipients at high risk for delayed graft function.[105,106] Since delayed graft function is predictive for poor long-term results,[5] it might be assumed that primary sirolimus-based immunosuppression will translate into improved long-term function in the future. On the other hand, recent experimental[107] and clinical[108,109] investigations with sirolimus revealed a delayed recovery of renal allografts from ischaemic and reperfusion injury. The prolongation of renal recovery with sirolimus is thought to be because of its antiproliferative and pro-apoptotic effects on renal tubular cells.[110]

From a multicentre trial of early ciclosporin withdrawal and sirolimus maintenance therapy including 525 recipients, 2-year and preliminary 3-year results have been reported.[94,111] At 3 years, serum creatinine was significantly lower and GFR was significantly higher in the patients who had had ciclosporin withdrawn compared with those who continued to receive ciclosporin. The incidence of death, rate of acute rejection episodes and the graft survival rate were not significantly different between both study arms at 2 and 3 years. At present, the role of sirolimus in long-term maintenance immunosuppression beyond 5 years cannot be assessed.

6. Summary and Conclusions

Long-term immunosuppressive maintenance therapy aims to prevent late acute rejection and the development and progression of chronic allograft nephropathy. The incidence of acute rejection episodes was significantly reduced by the introduction of calcineurin inhibitors into the post-transplant drug regimens and further improved by the use of MMF instead of azathioprine. Tacrolimus contributed an additional benefit in the prevention and treatment of corticosteroid-resistant rejection, minimising the need for rejection therapy with anti-CD3 antibodies.

Much less progress has been achieved in the control of chronic allograft nephropathy (illustrated as an example in figures 1 and 2). Figure 1 shows calculation of the overall cadaveric kidney graft survival rates, censored for patient death, from the author's centre. There has been a significant improvement in 10-year outcome with the shift from dual therapy with azathioprine to dual therapy with ciclosporin and a further benefit of triple therapy regardless of whether azathioprine or MMF was used. However, these improvements are mainly achieved in the early phase, during the first year after transplantation. When only recipients with graft function at 1 year are included in the calcula-

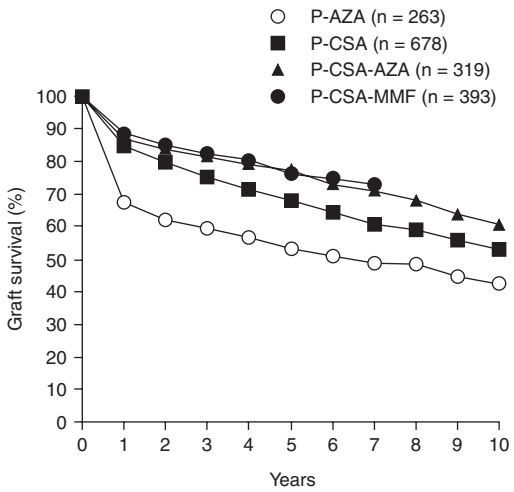

Fig. 1. Overall graft survival rates in 1653 cadaveric kidney transplantations, censored for patient death, according to intent-to-treat immunosuppressive maintenance regimen. Log-rank tests: P-AZA vs P-CSA, $p < 0.001$; P-AZA vs P-CSA-AZA, $p < 0.001$; P-AZA vs P-CSA-MMF, $p < 0.001$; P-CSA vs P-CSA-AZA, $p < 0.025$; P-CSA vs P-CSA-MMF, $p < 0.01$; P-CSA-AZA vs P-CSA-MMF, $p > 0.05$ (not significant). **AZA** = azathioprine; **CSA** = ciclosporin; **MMF** = mycophenolate mofetil; **P** = prednisone (or prednisolone).

tion (figure 2) the improvement is much smaller and only significant for patients receiving triple therapy. Beyond 5 years a nonsignificant trend for better graft half-life with MMF appears and dual therapy seems to be the less favourable option for long-term outcome. Historical single-centre data are no proof of concept, but they illustrate and confirm what was to be expected from controlled trials of up to 5 years' duration.

Chronic allograft nephropathy is the major cause of late graft losses besides death of recipients with graft function. It describes fibrosclerotic changes in long-surviving renal transplants, which are considered to result from immune injury and non-immune, mostly vascular, risk factors.[112,113] Two recent reviews considering histological findings[114] and immune responses[115] in chronic allograft nephropathy underline that progressive deterioration of renal graft function is mainly caused by chronic rejection and less by non-immune factors. Currently used long-term immunosuppressive regimens do not prevent or control these chronic immune processes sufficiently.

From the controlled trials summarised in this overview, there is no really convincing evidence that one drug regimen stands out as superior for long-term use. Triple therapy is used by many centres, but has not been shown to be significantly superior to dual therapy for long-term maintenance in controlled trials. Whether more favourable cardiovascular risk profiles of new immunosuppressive drugs translate into improved patient survival and reduced graft loss by death of recipients remains to be demonstrated. However, the periods of observation might be too short and the numbers at risk too small to draw any conclusions. The projected half-lives for the long-term combination of tacrolimus with MMF look promising but also need to be confirmed by long-term observations.

Clinicians in the care of kidney transplant patients have to make decisions on the basis of the drugs that are presently available and what is known about the effects of the drugs at this time. In the current situation, it seems unjustified to convert a patient with stable graft function and tolerable ad-

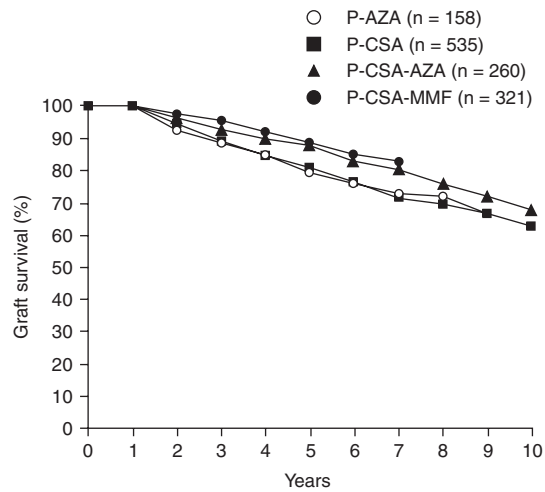

Fig. 2. Graft survival rates in 1274 cadaveric kidney transplantations with graft function at 1 year, censored for patient death, according to intent-to-treat immunosuppressive maintenance regimen. Graft half-lives (years): P-AZA = 13.1; P-CSA = 12.7; P-CSA-AZA = 14.3; P-CSA-MMF = 16.5. Log-rank tests: P-AZA vs P-CSA, $p > 0.05$ (ns); P-AZA vs P-CSA-AZA, $p > 0.05$ (ns); P-AZA vs P-CSA-MMF, $p < 0.05$; P-CSA vs P-CSA-AZA, $p > 0.05$ (ns); P-CSA vs P-CSA-MMF, $p < 0.01$; P-CSA-AZA vs P-CSA-MMF, $p > 0.05$ (ns). **AZA** = azathioprine; **CSA** = ciclosporin; **MMF** = mycophenolate mofetil; **ns** = not significant; **P** = prednisone (or prednisolone).

verse effects from one drug to another solely in expectation of future benefits. Acute early or late rejection episodes and intolerable adverse effects are a good reason for conversions between calcineurin inhibitors or inhibitors of purine metabolism. Slowly deteriorating graft function remains an unresolved problem.

Withdrawal of drugs, especially from triple therapy, is an option in a number of patients but always carries the risk of rejection. The risk seems to be highest after corticosteroid withdrawal and lower after cessation of azathioprine or MMF. The patients' attitudes towards withdrawal have been assessed by a Canadian group.[116] On the assumption of a 'risk-free choice', 65% of the patients would like to discontinue corticosteroids, 19% calcineurin inhibitors and 16% azathioprine or MMF. Unfortunately, the patients' preferences inversely correlate with the results of clinical studies reported in the literature.

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References

1. Ojo AO, Hanson JA, Wolfe RA, et al. Long-term survival in renal transplant recipients with graft function. Kidney Int 2000; 57: 307-13
2. First MR, Peddi VR, Weiskittel P, et al. Control of risk factors for cardiovascular disease in long-term renal transplant recipients. Transplant Proc 2001; 33: 3674-5
3. Boucher A, Masse M, Lauzon L, et al. Impact of immunosuppressive regimen on cardiovascular risk factors in kidney transplant recipients. Transplant Proc 2002; 34: 1799-802
4. Krämer BK, Zülke C, Kammerl MC, et al. Cardiovascular risk factors and estimated risk for CAD in a randomized trial comparing calcineurin inhibitors in renal transplantation: the European Tacrolimus vs Cyclosporine Microemulsion Study Group. Am J Transplant 2003; 3: 982-7
5. Gjertson DW. Impact of delayed graft function and acute rejection on graft survival. Transplant Proc 2002; 34: 2432
6. First MR. Renal function as a predictor of long-term graft survival in renal transplant patients. Nephrol Dial Transplant 2003; 18 Suppl. 1: 13-6
7. Paraskevas S, Kandaswamy R, Humar A, et al. Predicting long-term kidney graft survival: can new trials be performed? Transplantation 2003; 75: 1256-9
8. de Bruijne MHJ, Sijpkens YWJ, Paul LC, et al. Predicting kidney graft failure using time-dependent renal function covariates. J Clin Epidemiol 2003; 56: 448-55
9. Kaplan B, Schold J, Meier-Kriesche HU. Poor predictive value of serum creatinine for renal allograft loss. Am J Transplant 2003; 3: 1560-5
10. Grimm PC, Nickerson P, Gough J, et al. Computerized image analysis of Sirius Red-stained renal graft biopsies as a surrogate marker to predict long-term allograft function. J Am Soc Nephrol 2003; 14: 1662-8
11. Yilmaz S, Tomlanovich S, Mathew T, et al. Protocol core needle biopsy and histologic chronic allograft damage index (CADI) as surrogate end point for long-term graft survival in multicenter studies. J Am Soc Nephrol 2003; 14: 773-9
12. Ort D, Kovac W, Debol C. Adrenal cortex. In: Wilson J, Foster D, Kronenberg HM, editors. Williams textbook of endocrinology. 9th ed. Philadelphia (PA): WB Saunders, 1998: 517-604
13. Lerut JP. Avoiding steroids in solid organ transplantation. Transplant Int 2003; 16: 213-24
14. Calne RY. Twenty years' experience of immunosuppression in organ transplantation. Transplant Proc 1982; 14: 91-7
15. Allison AC, Eugui EM. Mycophenolate mofetil and its mechanisms of action. Immunopharmacology 2000; 47: 85-118
16. Borel JF. Mechanism of action of cyclosporin A and rationale use in nephrotic syndrome. Clin Nephrol 1991; 35 Suppl. 1: S23-30
17. Schreiber SL, Crabtree GR. The mechanism of action of cyclosporin A and FK506. Immunol Today 1992; 13: 36-42
18. Keown P, Niese D. Cyclosporine microemulsion increases drug exposure and reduces acute rejection without incremental toxicity in *de novo* renal transplantation: International Sandimmun Neoral Study Group. Kidney Int 1998; 54: 938-44
19. Pollard SG, Lear PA, Ready AR, et al. Comparison of microemulsion and conventional formulations of cyclosporine A in preventing acute rejection in *de novo* kidney transplant patients: the UK Neoral Renal Study Group. Transplantation 1999; 68: 1325-31
20. Peters DH, Fitton A, Plosker AF, et al. Tacrolimus: a review of its pharmacology, and therapeutic potential in hepatic and renal transplantation. Drugs 1993; 46: 746-94
21. Sehgal SN. Rapamune (RAPA, rapamycin, sirolimus): mechanism of action immunosuppressive effect results from blockade of signal transduction and inhibition of cell cycle progression. Clin Biochem 1998; 31: 335-40
22. Taylor HE, Ackman CF, Horowitz I. Canadian clinical trial of antilymphocyte globuline in human cadaver renal transplantation. Can Med Assoc J 1976; 115: 1205-8
23. Bonnefoy-Berard N, Vincent C, Revillard J-P. Antibodies against functional leukocyte surface molecules in polyclonal antilymphocyte and antithymocyte globulins. Transplantation 1991; 51: 669-73
24. Soulillou JP. Relevant targets for therapy with monoclonal antibodies in allograft transplantation. Kidney Int 1994; 46: 540-53
25. Helderman JH. Review and preview of anti-T-cell antibodies. Transplant Proc 1995; 27: 8-9
26. The Canadian Multicentre Transplant Study Group. A randomized clinical trial of cyclosporine in cadaveric renal transplantation: analysis at three years. N Engl J Med 1986; 314: 1219-25
27. Calne RY, for the European Multicentre Trial Group. Cyclosporin in cadaveric renal transplantation: 5-year follow-up of a multicenter trial. Lancet 1987; 330: 506-7
28. Hariharan S, Johnson CP, Breshnahan BA, et al. Improved graft survival after renal transplantation in the United States, 1988 to 1996. N Engl J Med 2000; 342: 605-12

29. Meier-Kriesche H-U, Ojo AO, Port FK, et al. Survival improvement among patients with end-stage renal disease: trends over time for transplant recipients and wait-list patients. J Am Soc Nephrol 2001; 12: 1293-6
30. Ferguson RM, Henry ML, Elkhammas EA, et al. Twenty years of renal transplantation at Ohio State University: the results of five areas of immunosuppression. Am J Surg 2003; 186: 306-11
31. Ponticelli C, Villa M, Cesana B, et al. Risk factors for late kidney allograft failure. Kidney Int 2002; 62: 1848-54
32. Pascual M, Theruvath T, Kawai T, et al. Strategies to improve long-term outcome after renal transplantation. N Engl J Med 2002; 346: 580-90
33. Beveridge T, Calne RY. Cyclosporine (Sandimmun) in cadaveric renal transplantation: ten-year follow-up of a multicenter trial: European Multicentre Trial Group. Transplantation 1995; 59: 1568-70
34. Ponticelli C, Civati G, Tarantino A, et al. Randomized study with cyclosporine in kidney transplantation: 10-year follow-up. Am Soc Nephrol 1996; 7: 792-7
35. Knight RJ, Kerman RH, Welsh M, et al. Chronic rejection in primary allograft recipients under cyclosporine-prednisone immunosuppressive therapy. Transplantation 1991; 51: 355-9
36. Marcen R, Pascual J, Teruel JL, et al. Outcome of cadaveric renal transplant patients treated for 10 years with cyclosporine: is chronic allograft nephropathy the major cause of late graft loss? Transplantation 2001; 72: 57-62
37. Grimbert P, Baron C, Fruchaud G, et al. Long-term results of a prospective randomised study comparing two immunosuppressive regimens, one with and one without CsA, in low risk renal transplant recipients. Transplant Int 2002; 15: 550-5
38. Helderman JH, van Buren DH, Amend WJC, et al. Chronic immunosuppression of the renal transplant patient. J Am Soc Nephrol 1994; 4: S2-9
39. Montagnino G, Tarantino A, Segolini GP, et al. Long-term results of a randomized study comparing three immunosuppressive schedules with cyclosporine in cadaveric kidney transplantation. J Am Soc Nephrol 2001; 12: 2163-9
40. Nishikawa E, Terasaki PI. Annual trends in kidney transplantation. Clin Transpl 2001; 15: 247-69
41. Stoves J, Newstead CG. Variability of cyclosporine exposure and its relevance to chronic allograft nephropathy: a case control study. Transplantation 2002; 74: 1794-7
42. Marcen R, Pascual J, Tato A, et al. Comparison of C0 and C2 cyclosporine monitoring in long-term renal transplant recipients. Transplant Proc 2003; 35: 1780-2
43. Shapiro R, Jordan M, Scantlebury V, et al. A prospective, randomized trial of FK-506 in renal transplantation: a comparison between double- and triple-drug therapy. Clin Transplant 1994; 8: 508-15
44. Chang RWS, Snowdon S, Palmer A, et al. European randomized trial of dual versus triple tacrolimus-based regimens for control of acute rejection in renal allograft recipients. Transplant Int 2001; 14: 384-90
45. Pascual J, Ortuno J, for the Spanish and Italian Tacrolimus Study Group. Simple tacrolimus-based immunosuppressive regimens following renal transplantation: a large multicenter comparison between double and triple therapy. Transplant Proc 2002; 34: 89-91
46. Garcia I, for the Spanish and Italian Tacrolimus Study Group. Efficacy and safety of dual versus triple tacrolimus-based therapy in kidney transplantation: two-year follow up. Transplant Proc 2002; 34: 1638-9
47. Pascual J, Segoloni G, Gonzales Molina M, et al. Comparison between a two-drug regimen with tacrolimus and steroids and a triple one with azathioprine in kidney transplantation: results of a European trial with 3-year follow up. Transplant Proc 2003; 35: 1701-3
48. Pirsch JD, Miller J, Deierhoi MH, et al. A comparison of tacrolimus (FK506) and cyclosporine for immunosuppression after cadaveric renal transplantation. Transplantation 1997; 63: 977-83
49. Jensik SC; the FK 506 Kidney Transplant Study Group. Tacrolimus (FK 506) in kidney transplantation: three year survival results of the US multicenter, randomized, comparative trial. Transplant Proc 1988; 30: 1216-8
50. Meier-Kriesche HU, Kaplan B. Cyclosporine microemulsion and tacrolimus are associated with decreased chronic allograft failure and improved long-term graft survival as compared with Sandimmune. Am J Transplant 2002; 2: 100-4
51. Murphy GJ, Waller JR, Sandford RS, et al. Randomized clinical trial of the effect of microemulsion cyclosporin and tacrolimus on renal allograft fibrosis. Br J Surg 2003; 90: 680-6
52. Pascual J, Marcén R, Burgos FJ, et al. One-center comparison between primary immunosuppression based on Neoral cyclosporin and tacrolimus for renal transplantation. Transplant Proc 2002; 34: 94-5
53. Jurewicz WA. Tacrolimus versus cyclosporin immunosuppression: long-term outcome in renal transplantation. Nephrol Dial Transplant 2003; 18 Suppl. 1: 7-11
54. Vincenti F, Jensik SC, Filo RS, et al. A long-term comparison of tacrolimus (FK506) and cyclosporine in kidney transplantation: evidence for improved allograft survival at five years. Transplantation 2002; 73: 775-82
55. Mayer AD. Chronic rejection and graft half-life: five-year follow-up of the European tacrolimus multicenter renal study. Transplant Proc 2002; 34: 1491-2
56. Neu AM, Ho PL, Fine RN, et al. Tacrolimus vs cyclosporine A as primary immunosuppression in pediatric renal transplantation: a NAPRTCS study. Pediatr Transplant 2003; 7: 217-22
57. Claesson K, Mayer AD, Squifflet J-P, et al. Lipoprotein patterns in renal transplant patients: a comparison between FK 506 and cyclosporine A patients. Transplant Proc 1998; 30: 1292-4
58. Friemann S, Feurig E, Padberg W, et al. Improvement of nephrotoxicity, hypertension, and lipid metabolism after conversion of kidney transplant recipients from cyclosporine to tacrolimus. Transplant Proc 1998; 30: 1240-2
59. McCune TR, Thacker II LR, Peters TG, et al. Effects of tacrolimus on hyperlipidemia after successful renal transplantation. Transplantation 1998; 65: 87-92
60. Copley JB, Staffeld C, Lindberg J, et al. Cyclosporine to tacrolimus: effect on hypertension and lipid profiles in renal allografts. Transplant Proc 1998; 30: 1254-6
61. Ligtenberg G, Hené RJ, Blankestijn PJ, et al. Cardiovascular risk factors in renal transplant patients: cyclosporin A versus tacrolimus. J Am Soc Nephrol 2001; 12: 368-73
62. Thorp M, DeMattos A, Bennett W, et al. The effect of conversion from cyclosporine to tacrolimus on gingival hyperplasia, hirsutism and cholesterol. Transplantation 2000; 69: 1218-24
63. Maes BD, Kuypers D, Messiaen T, et al. Posttransplantation diabetes mellitus in FK-506-treated renal transplant recipients: analysis of incidence and risk factors. Transplantation 2001; 72: 1655-61

64. Binet I, Nickeleit V, Hirsch HH, et al. Polyoma virus disease under new immunosuppressive drugs: a cause of renal graft dysfunction and graft loss. Transplantation 1999; 67: 918-22
65. Lazzaro C, McKechnie T, McKenna M. Tacrolimus versus cyclosporin in renal transplantation in Italy: cost-minimisation and cost-effectiveness analyses. J Nephrol 2002; 15: 580-8
66. Scott LJ, McKeage K, Keam SJ, et al. Tacrolimus: a further update of its use in the management of organ transplantation. Drugs 2003; 63 (12): 1247-97
67. Tanabe K. Calcineurin inhibitors in renal transplantation: what is the best option? Drugs 2003; 63 (15): 1535-48
68. Vanrenterghem Y. Vascular rejection with tacrolimus and potential long-term graft outcome. Transplant Proc 1999; 31 Suppl. 7A: 86S-7S
69. Briggs D, Dudley C, Pattison J, et al. Effects of immediate switch from cyclosporine microemulsion to tacrolimus at first acute rejection in renal allograft recipients: European Tacrolimus Renal Rejection Study Group. Transplantation 2003; 75: 2058-63
70. European Mycophenolate Mofetil Cooperative Study Group. Placebo-controlled study of mycophenolate mofetil combined with cyclosporine and corticosteroids for prevention of acute rejection. Lancet 1995; 345: 1321-5
71. The Tricontinental Mycophenolate Mofetil Renal Transplantation Study Group. A blinded, randomized clinical trial of mycophenolate mofetil for the prevention of acute rejection in cadaveric renal transplantation. Transplantation 1996; 61: 1029-37
72. The US Mycophenolate Mofetil Study Group. Mycophenolate mofetil for the prevention of acute rejection of primary cadaveric kidney transplants: status of the MYC 1866 study at 1 year. Transplant Proc 1997; 29: 348-9
73. European Mycophenolate Mofetil Cooperative Study Group. Mycophenolate mofetil in renal transplantation: 3-year results from the placebo-controlled trial. Transplantation 1999; 68: 391-6
74. US Renal Transplant Mycophenolate Mofetil Study Group. Mycophenolate mofetil in cadaveric renal transplantation. Am J Kidney Dis 1999; 34: 296-303
75. Mathew TH. A blinded long-term, randomized multicenter study of mycophenolate mofetil in cadaveric renal transplantation: results at three years: Mycophenolate Mofetil Renal Transplantation Study Group. Transplantation 1998; 65: 1450-4
76. Meier-Kriesche H-U, Steffen BJ, Hochberg AM, et al. Mycophenolate mofetil versus azathioprine therapy is associated with a significant protection against long-term renal allograft function deterioration. Transplantation 2003; 75: 1341-6
77. Meier-Kriesche H-U, Ojo AO, Leichtman AB, et al. Effect of mycophenolate mofetil on long-term outcomes in African American renal transplant recipients. J Am Soc Nephrol 2000; 11: 2366-70
78. Ojo AO, Meier-Kriesche H-U, Hanson JA, et al. Mycophenolate mofetil reduces late renal allograft loss independent of acute rejection. Transplantation 2000; 69: 2405-9
79. Offermann G. Five-year results of renal transplantation on immunosuppressive triple therapy with mycophenolate mofetil. Clin Transplant 2003; 17: 43-6
80. Tuncer M, Gürkan A, Erdogan O, et al. Mycophenolate mofetil in renal transplantation: five years experience. Transplant Proc 2002; 34: 2087-8
81. van Hooff JP, Squifflet J-P, Vanrenterghem Y. Benelux experience with a combination of tacrolimus and mycophenolate mofetil: 4-year results. Transplant Proc 2002; 34: 1591-3
82. Johnson C, Ahsan N, Gonwa T, et al. Randomized trial of tacrolimus (Prograf) in combination with azathioprine or mycophenolate mofetil versus cyclosporine (Neoral) with mycophenolate mofetil after cadaveric kidney transplantation. Transplantation 2000; 69: 834-41
83. Gonwa T, Johnson C, Ahsan N, et al. Randomized trial of tacrolimus + mycophenolate mofetil or azathioprine versus cyclosporine + mycophenolate mofetil after cadaveric kidney transplantation: results at three years. Transplantation 2003; 75: 2048-53
84. Pascual M, Curtis J, Delmonico FL, et al. A prospective, randomized clinical trial of cyclosporine reduction in stable patients greater than 12 months after renal transplantation. Transplantation 2003; 75: 1501-5
85. Gotti E, Perico N, Perna A, et al. Renal transplantation: can we reduce calcineurin inhibitor/stop steroids? J Am Soc Nephrol 2003; 14: 755-66
86. Opelz G, Dohler B. Cyclosporine and long-term kidney graft survival. Transplantation 2001; 72: 1267-73
87. Kasiske BL, Chakkera HA, Louis TA, et al. A meta-analysis of immunosuppression withdrawal trials in renal transplantation. J Am Soc Nephrol 2000; 11: 1910-7
88. McPhee IA, Bradley JA, Briggs JD, et al. Long-term outcome of a prospective randomized trial of conversion from cyclosporine to azathioprine treatment one year after transplantation. Transplantation 1998; 66: 1186-92
89. Kumar DD, Srivastava A, Mandhani A, et al. Cyclosporin A withdrawal in live related renal transplantation: long-term results. Clin Transplant 2001; 15: 136-41
90. Bakker RC, Hollander AAMJ, Mallat MJK, et al. Conversion from cyclosporine to azathioprine at three months reduces the incidence of chronic allograft nephropathy. Kidney Int 2003; 64: 1027-34
91. Smak Gregoor PJH, de Sévaux RGL, Ligtenberg G, et al. Withdrawal of cyclosporine or prednisone six months after kidney transplantation in patients on triple drug therapy: a randomized, prospective, multicenter study. J Am Soc Nephrol 2002; 13: 1365-73
92. Abramowicz D, Manas D, Lao M, et al. Cyclosporin withdrawal from a mycophenolate containing immunosuppressive regimen in stable kidney transplant recipients: a randomized, controlled study. Transplantation 2002; 74: 1725-34
93. Kuypers DRJ, Evenepoel P, Maes B, et al. The use of an anti-CD25 monoclonal antibody and mycophenolate mofetil enables the use of a low-dose tacrolimus and early withdrawal of steroids in renal transplant recipients. Clin Transplant 2002; 17: 234-41
94. Oberbauer R, Kreis H, Johnson RW, et al. Long-term improvement in renal function with sirolimus after early cyclosporine withdrawal in renal transplant recipients: 2-year results of the Rapamune Maintenance Regimen Study: Rapamune Maintenance Regimen Study Group. Transplantation 2003; 76: 364-70
95. Saunders RN, Bicknell GR, Nicholson ML. The impact of cyclosporine dose reduction with or without the addition of rapamycin on functional, molecular, and histological markers of chronic allograft nephropathy. Transplantation 2003; 75: 772-80
96. Gauthier P, Helderman JH. Cyclosporine avoidance. J Am Soc Nephrol 2000; 11: 1933-6

97. Vincente F. Sparing of calcineurin antagonists: the use of interleukin-2 monoclonal antibodies in conjunction with mycophenolate mofetil. Transplant Immunol Lett 2000; 16: 4-6
98. Tran HTB, Acharya MK, Mckay DB, et al. Avoidance of cyclosporine in renal transplantation: effects of daclizumab, mycophenolate mofetil, and steroids. J Am Soc Nephrol 2000; 11: 1903-9
99. Offermann G, Krause PH, Johann D, et al. Late conversion from steroids to azathioprine in cyclosporin-treated renal graft recipients. Transplant Int 1989; 2: 108-12
100. Schulak JA, Mayes JT, Moritz CE, et al. A prospective randomized trial of prednisone versus no prednisone maintenance therapy in cyclosporine-treated and azathioprine-treated renal transplant patients. Transplantation 1990; 49: 327-32
101. Offermann G, Schwarz A, Krause P-H. Long-term effects of steroid withdrawal in kidney transplantation. Transplant Int 1993; 6: 290-2
102. Sivaraman P, Nussbaumer G, Landsberg D. Lack of long-term benefits of steroid withdrawal in renal transplant recipients. Am J Kidney Dis 2001; 37: 1162-9
103. Jensen S, Jackson EC, Riley L, et al. Tacrolimus-based immunosuppression with steroid withdrawal in pediatric kidney transplantation: 4 year experience at a moderate-volume center. Pediatr Transplant 2003; 7: 119-24
104. Birkeland SA. Steroid-free immunosuppression in renal transplantation: a long-term follow up of 100 consecutive patients. Transplantation 2001; 71: 1089-90
105. Hong JC, Kahan BD. Use of anti-CD25 monoclonal antibody in combination with rapamycin to eliminate cyclosporine treatment during the induction phase of immunosuppression. Transplantation 1999; 68: 701-4
106. Shaffer D, Langone A, Nylander WA, et al. A pilot protocol of marginal donor kidneys or with delayed graft function. Clin Transplant 2003; 17 Suppl. 9: 31-4
107. Fuller TF, Freise CE, Serkova N, et al. Sirolimus delays recovery of rat kidney transplants after ischemia-reperfusion injury. Transplantation 2003; 76: 1594-9
108. McTaggart RA, Gottlieb D, Brooks J, et al. Sirolimus prolongs recovery from delayed graft function after cadaveric renal transplantation. Am J Transplant 2003; 3: 416-23
109. Smith KD, Wrenshall LE, Nicosia RF, et al. Delayed graft function and cast nephropathy associated with tacrolimus plus rapamycin use. J Am Soc Nephrol 2003; 14: 1037-45
110. Davies C. Sirolimus delays renal allograft recovery. Am J Transplant 2003; 3: 363-5
111. Oberbauer R, Kreis H, Campistol JM, et al. Renal function improves significantly after early cyclosporine withdrawal in sirolimus-treated renal transplant recipients: 3-year results of the Rapamune Maintenance Regimen (RMR) Trial [abstract]. J Am Soc Nephrol 2003; 14: 10A
112. Paul LC. Chronic allograft nephropathy: an update. Kidney Int 1999; 36: 783-93
113. Prommool S, Jhangri GS, Cockfield SM, et al. Time dependency of factors affecting renal allograft survival. J Am Soc Nephrol 2000; 11: 565-73
114. Sijpkens YWJ, Doxiades IIN, van Kemnade FJ, et al. Chronic rejection with or without transplant vasculopathy. Clin Transplant 2003; 17: 163-70
115. Joosten SA, van Kooten C, Paul LC. Pathogenesis of chronic allograft rejection. Transplant Int 2003; 16: 137-45
116. Prasad GVR, Nash MM, McFarlane PA, et al. Renal transplant recipient attitudes toward steroid use and steroid withdrawal. Clin Transplant 2003; 17: 135-9

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