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Calcineurin Inhibitors in Renal Transplantation

What is the Best Option?

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Abstract

Recently, new calcineurin inhibitors, such as tacrolimus (FK-506) and microemulsion cyclosporin, have been approved for maintenance immunosuppression in renal transplant recipients and short-term outcomes have been accumulating. In the majority of patients, these calcineurin inhibitors have been used in combination with new immunosuppressive drugs, such as mycophenolate mofetil (MMF) or sirolimus.

Under these circumstances, a comparison of cyclosporin and tacrolimus provides the answer to a very important controversial issue. Which drug should we choose in individual patients? In an attempt to answer this question, this review compared the use of tacrolimus and cyclosporin in modern immunosuppressive regimens, which have already been published in well designed clinical studies, and discusses how immunosuppression should be individualised in renal transplant patients.

Overall, short-term patient and graft survival with cyclosporin microemulsion and tacrolimus is almost identical. The incidence of acute rejection is generally lower in tacrolimus/azathioprine- than in cyclosporin/azathioprine-treated patients. However, in conjunction with MMF, the difference in the incidence of acute rejection between tacrolimus- and cyclosporin-treated patients became smaller. Adverse events, such as hypertension, hyperlipidaemia and cosmetic changes (gum hypertrophy, hirsutism) seem to be less frequent in tacrolimus-treated than in cyclosporin-treated patients. Recent randomised studies showed that the incidence of post-transplant diabetes mellitus was almost identical between low-dose tacrolimus- and cyclosporin-treated patients.

According to the data discussed in this review, the recommendation on the choice of calcineurin inhibitors at this moment is that either cyclosporin or tacrolimus can be used safely and effectively for patients without any risk factors. However, at our centre, we prefer tacrolimus to cyclosporin in patients with a high risk for rejection, such as those with ABO-incompatibility, delayed graft function, sensitisation, and African American race and some other risk factors, such as hypertension and hyperlipidaemia. Moreover, tacrolimus may be preferable to cyclosporin for women because of hirsutism and for children because of the steroid-sparing effect. We consider that cyclosporin should be chosen when

patients experience tacrolimus-related adverse events, such as severe chest pain, tremor, gastrointestinal symptoms and encephalopathy.

In conclusion, well tolerated and effective immunosuppression is feasible with both cyclosporin and tacrolimus. In the current immunosuppressive regimens, a calcineurin inhibitor, either tacrolimus or cyclosporin, is the essential basic standard immunosuppressant. Clinicians need to decide the best means of optimising therapy for individual patients, based on various risk factors, such as risk of rejection, i.e. sensitisation, delayed graft function and ABO-incompatibility, and some adverse events, such as hypertension, hyperlipidaemia and cosmetic changes.

Since the early 1980s, cyclosporin has been the most important immunosuppressive agent employed in renal transplantation and its use has led to a dramatic improvement in the success of organ transplants.[1-3] Recently, tacrolimus (FK-506), mycophenolate mofetil (MMF), sirolimus (rapamycin) and microemulsion cyclosporin have been approved for maintenance immunosuppression in renal transplant recipients and short-term outcomes have been accumulating. The early experiences of tacrolimus indicated that it might be a more potent immunosuppressant than cyclosporin according to the short-term results. However, some adverse events, such as diabetogenicity and neurotoxicity, occurred much more frequently with tacrolimus than cyclosporin recipients. In addition, the long-term outcome of a large number of tacrolimus-treated renal transplant recipients was not yet available.

On the other hand, since MMF was introduced for clinical use, the outcome of renal transplantation has improved in both tacrolimus- and cyclosporin-treated transplant recipients.[4-9] Under these circumstances, a comparison of cyclosporin and tacrolimus provides the answer to very important controversial issues. Which drug is a more potent immunosuppressant? Which drug has more adverse effects? Which drug should we choose in individual patients? In an attempt to answer these questions, this review compares the use of tacrolimus and cyclosporin use in modern immunosuppressive regimens, which have already been published in well designed clinical studies, and discusses how immunosuppression should be individualised in renal transplant patients.

Modern immunosuppressive regimens studied and included in this review are cyclosporin or tacrolimus in combination with azathioprine, MMF or sirolimus. FTY-720 is a promising agent currently underdevelopment; however, no data from large randomised trials have been reported to date and so it is not included in this discussion of comparative data.

1. The Literature Search and Evaluation Methods

Most of the well-designed, randomised comparative studies between tacrolimus and cyclosporin were published between 1995 and 2002, because the use of tacrolimus for transplantation of various organs worldwide began during this period. Where possible, randomised studies comparing tacrolimus and cyclosporin are cited in this article; however, in some sections, non-randomised studies are described since no pertinent well-designed, randomised study was available. To this end, Medline was searched from 1990 to 2002.

2. Cyclosporin or Tacrolimus in Combination with Azathioprine

Studies comparing the immunosuppressive effects of cyclosporin with azathioprine and tacrolimus with azathioprine are shown in table I and table II.

Tacrolimus was first isolated in 1985 from the fermentation broth of *Streptomyces tsukubaensis*.[10,11] It has potent inhibitory effects on T lymphocyte activation and binds specifically to FK-506

Table I. Comparative trials of cyclosporin versus tacrolimus in renal transplant recipients

Therapy	Pirsch et al.[4] (%)	Mayer et al.[5] (%)	Johnson et al.[6] (%)[a]	Ahsan et al.[7] (%)[a]	Squifflet et al.[8] (%)	Margreiter et al.[9] (%)[a]
Acute rejection (steroid-resistant)						
CYA/AZ	46.4 (25.1)	54.5 (20.7)				51.3 (21.0)
CYA/MMF			20 (11)	22.7 (12)		
FK/AZ	30.7 (10.7)	32.3 (10.2)	17 (12)	18.4 (13.2)	46.3 (15.9)	32.5 (9.4)
FK/MMF			15 (4)	16.7 (5.6)	23 (4)	
Graft survival						
CYA/AZ	87.9[b]	86.2[b]				91.9[c]
CYA/MMF			70[b]	76.7[d]		
FK/AZ	91.2[b]	82.5[b]	80[b]	84.2[d]	90.2[c]	94.8[c]
FK/MMF			88[b]	82.8[d]	95[c]	
PTDM[e]						
CYA/AZ	4.0	2.1				2.0
CYA/MMF			6.5	6.5		
FK/AZ	19.9	11.6	12.3	7.0	0.0	4.5
FK/MMF			2.2	8.7	4.5	

a Cyclosporin microemulsion formulation used.

b 12 months.

c 6 months.

d 24 months.

e Type 1 (insulin-dependent) diabetes mellitus.

AZ = azathioprine; **CYA** = cyclosporin; **FK** = tacrolimus; **MMF** = mycophenolate mofetil; **PTDM** = post-transplant diabetes mellitus.

binding proteins in the cytoplasm. At an *in vitro* concentration 10–100 times less than that required for cyclosporin, tacrolimus inhibits transcription of the early T cell activation genes for interleukin (IL)-2 and other cytokines.[12-18]

Multicentre, randomised studies comparing the conventional formulation of cyclosporin with tacrolimus have been conducted in the US and Europe.[5,19,20] In the US study, 412 patients received either cyclosporin or tacrolimus with antithymocyte globulin, corticosteroids and azathioprine. After 1 year, the incidence of biopsy-proven rejection was 30.7% in the tacrolimus group and 46.4% in the cyclosporin group ($p = 0.001$).[19]

The 3-year results of this study failed to show a significant difference in graft survival between the two groups: 81.9 and 77.8% in the tacrolimus and cyclosporin groups, respectively ($p = 0.405$). However, of the 205 patients who received cyclosporin therapy as primary immunosuppression, 17% were changed to tacrolimus because of refractory rejection. In contrast, only 8.2% of patients in the tacrolimus group were switched to cyclosporin, and the reasons for the change were adverse events rather than rejection in most of the patients. When crossover for rejection was counted as graft failure, the 3-year graft survival rate was 81.5% for the tacrolimus group and 70% for cyclosporin ($p < 0.005$). Tacrolimus-treated patients showed a reduced need for antihypertensive medications in the 3-year study. Of the 30 tacrolimus-treated patients (14%) who developed posttransplant diabetes mellitus, 10 patients no longer needed insulin therapy at 3 years.[20,21]

Recently, 5-year outcomes have been reported, and intent-to-treat analysis revealed equivalent patient and graft survival between treatment arms at 5 years of follow-up (79.1 vs 81.4%; $p = 0.472$ and 64.3 vs 61.6%; $p = 0.558$ among tacrolimus- and cyclosporin-treated patients, respectively). The authors concluded that graft survival was significantly improved in the tacrolimus treatment arm when crossover due to rejection was counted as graft failure (63.8 vs 53.8%; $p = 0.014$). However, as

already pointed out by the authors, immunosuppressive agents introduced since their present clinical trial was initiated have resulted in substantial change in the design of immunosuppressive regimens. In particular, in many participants of the trial the conventional formulation of cyclosporin and azathioprine were changed to a microemulsion formulation of cyclosporin and MMF, respectively. The changing of the immunosuppressive agents may have affected the outcome and may make it difficult to compare the immunosuppressive potency of tacrolimus and cyclosporin.[4,22,23]

In the European study,[5] 448 patients were randomised to receive cyclosporin as the conventional formulation, azathioprine and corticosteroids, or tacrolimus, azathioprine and corticosteroids without the induction with anti-lymphocyte globulin. The overall rate of rejection was 34.2 and 57.2% ($p < 0.001$) for the tacrolimus and cyclosporin groups, respectively. The graft survival rate was similar in the two groups at 82.5 versus 86.2% for the tacrolimus and cyclosporin arms, respectively ($p = 0.380$). As in the US study, more patients were switched from cyclosporin to tacrolimus than from tacrolimus to cyclosporin and for similar reasons.[5]

When cyclosporin microemulsion became available and provided improved pharmacokinetic properties, the European Renal Transplantation Study Group conducted a large, multicentre trial comparing tacrolimus and cyclosporin microemulsion in renal transplantation.[24,25] Five-hundred and sixty patients at 50 European centres were randomised to receive a triple regimen consisting of either tacrolimus ($n = 287$) or cyclosporin microemulsion ($n = 273$) concomitantly with azathioprine and corticosteroids.[9] The Kaplan-Meier estimates of patient survival (99.3 vs 98.5%) and graft survival (94.8 vs 91.9%) at 6 months after transplantation showed no statistically significant difference between the two groups. The incidence of biopsy-proven acute rejection was significantly lower in the tacrolimus group than in the cyclosporin microemulsion group (32.5 vs 51.3%; $p < 0.001$). The incidence of biopsy-proven corticosteroid-resistant rejection was also significantly lower in the tacrolimus group than in the cyclosporin microemulsion group (9.4 vs 21%; $p < 0.001$). In the tacrolimus group, one patient (0.3%) was switched to cyclosporin microemulsion treatment, while in the cyclosporin group, 27 patients (10%) were changed to tacrolimus following acute rejection ($p < 0.001$). In addition, the incidence of hypertension and hypercholesterolaemia was much more frequent in the cyclosporin group than in the tacrolimus group. Margreiter et al.[9] concluded that tacrolimus therapy proved to be superior to cyclosporin microemulsion-based therapy in preventing acute renal allograft rejection and in adverse events, such as hypertension and hypercholesterolaemia.[9,24,25]

Since azathioprine, which is an anti-metabolite, is no longer employed as a standard immunosuppressive agent in renal transplantation, these data should be carefully interpreted. The immunosuppressive effect of tacrolimus is probably more potent than that of cyclosporin, and when azathioprine was being widely used, we could see the difference between the two drugs. However in the MMF era, which is described in section 3, the difference between the two drugs has become smaller.

Table II. Comparison of outcomes and adverse events with tacrolimus versus cyclosporin in renal transplant recipients

Outcome	Tacrolimus vs cyclosporin
Patient survival (1-yr)	=
Graft survival (1-yr)	=
Acute rejection	
overall	<<
steroid-resistant	<<
Complications	
hypertension	<<
hyperuricaemia	=
Hyperlipidaemia	<<
Neurotoxicity	=
Tremor	=
Hypertricosis	<<
Gum hypertrophy	<<
Diabetes mellitus	≤
Nephrotoxicity	=

= indicates equal; ≤ indicates small difference; << indicates significant difference.

3. Cyclosporin or Tacrolimus with Mycophenolate Mofetil

Studies comparing immunosuppressive effects of cyclosporin with MMF and tacrolimus with MMF are shown in table I.

MMF is a highly selective, noncompetitive and reversible inhibitor of inosine monophosphate dehydrogenase (IMPDH), an essential enzyme in the *de novo* biosynthesis of guanine. Proliferating lymphocytes require both the *de novo* and salvage pathways for purine biosynthesis. Therefore, MMF is a potent inhibitor of both B and T lymphocyte proliferation.[20]

The US Renal Transplantation MMF Study Group,[26] the Tricontinental MMF Renal Transplant Study Group,[27] and the European MMF Cooperative Study Group[28] have already reported the outcome of their clinical trials independently. A pooled analysis of the three studies at 1 year showed a significant decrease in the incidence of acute rejection: 40.8% in the placebo-azathioprine group versus 16.9% in the 2g MMF group and 16.5% in the 3g MMF group.[20]

Although the 3-year results of the Tricontinental MMF Renal Transplant Study Group and the European MMF Cooperative Study Group failed to show significant differences in graft and patient survival, the significant reduction in acute rejection may contribute to improved long-term graft survival.[27,28] The Tricontinental MMF renal transplant study group showed that graft survival was 81.9, 84.8 and 80.2%, in the MMF 2g, MMF 3g and azathioprine groups, respectively. None of these differences were statistically significant. During the first 6 months, the incidence of biopsy-proven acute rejection was 19.7, 15.9 and 35.5% in the MMF 2g, MMF 3g and azathioprine groups, respectively. MMF groups showed significantly less biopsy-proven acute rejection than the azathioprine group.[27]

MMF therapy was found to be associated in a dose-dependent manner with increases in gastrointestinal and haematological adverse events, and a slightly higher incidence of infections. The incidence of tissue-invasive cytomegalovirus (CMV) disease and lymphoproliferative disease was also increased.[27,28]

In a multicentre, randomised trial of tacrolimus plus MMF, tacrolimus plus azathioprine, and cyclosporin microemulsion plus MMF, patient and graft survival rates were almost the same in all groups; the incidences of rejection were 15, 17 and 20%, respectively and the incidences of steroid-resistant rejection were 4, 12 and 11%, respectively.[6] These data suggest that tacrolimus plus MMF immunosuppression appears quite effective.

Ahsan et al.[7] recently reported their 2-year results of a similar randomised trial of tacrolimus plus MMF or tacrolimus plus azathioprine versus cyclosporin microemulsion plus MMF after cadaveric renal transplantation. Patient survival was 94.4 and 96.1% in the tacrolimus plus MMF and tacrolimus plus azathioprine treatment arms, respectively, and 88.0% in the cyclosporin group. Corresponding graft survival rates were 82.8, 84.2 and 76.7%, respectively. These authors reported that all three immunosuppressive regimens provided excellent safety and efficacy, and the best results overall were achieved with tacrolimus plus MMF. Namely, patients with delayed graft function/acute tubular necrosis who were treated with tacrolimus plus MMF experienced a 23% increase in allograft survival compared with patients receiving cyclosporin microemulsion plus MMF, and renal function at 2 years was better in the tacrolimus treatment groups compared with the cyclosporin microemulsion group.[7]

These authors also performed subset analysis of the outcome of African-American patients. They reported that acute rejection rates were higher in the African-American patients in all three groups compared with the overall rates; however, none of the African-American patients in the tacrolimus plus MMF group required antilymphocyte therapy for treatment of rejection.[7]

Squifflet et al.[8] tried dose optimisation of MMF in combination with low-dose tacrolimus and found that both 1g and 2g of MMF were associated with significantly lower rates of acute rejection compared with tacrolimus alone (24.1, 22.5 and 46.3% with

MMF 1g, MMF 2g and tacrolimus alone, respectively). Gastrointestinal adverse events and leucopenia were higher in the MMF groups, especially in the MMF 2g group. They concluded that low-dose tacrolimus combined with a MMF dose of 1g daily provided an optimised efficacy and safety profile.[8]

Recently, we reported that an excellent short-term outcome in ABO-incompatible renal transplantation was obtained by pretransplant administration of tacrolimus plus MMF from 6 days prior to renal transplantation. Namely, the 1-year graft survival was 100% and the incidence of acute rejection was only 11%, which was much better than that of historical control group data from patients treated with cyclosporin as the conventional formulation.[29]

4. Sirolimus and Calcineurin Inhibitors

Sirolimus, like tacrolimus, is a macrolide antibiotic with potent antilymphocyte activity. Unlike cyclosporin, it complexes with a different cytosolic immunophilin (FKBP12), resulting in suppression of cytokine-driven T-cell proliferation by inhibiting progression from the G1 to the S phase of the cell cycle.[30,31]

No large-scale, randomised study comparing cyclosporin plus sirolimus and tacrolimus plus sirolimus immunosuppression has been performed; however, well-designed, independently performed studies of cyclosporin plus sirolimus and tacrolimus plus sirolimus immunosuppression are available and can be used to compare the two calcineurin inhibitors in combination with sirolimus. In addition, since many authors try to eliminate the use of calcineurin inhibitors under sirolimus immunosuppression, this approach is briefly discussed.

Kahan et al.[32] conducted a prospective, multicentre, randomised, double-blind trial to investigate the impact of the addition of sirolimus, compared with azathioprine, to a cyclosporin microemulsion and prednisone regimen. After transplantation, 719 recipients of primary HLA-mismatched cadaveric or living donor renal allografts were randomly assigned to sirolimus 2mg (n = 284) or 5mg daily (n = 274), or azathioprine (n = 161). The rate of efficacy failure at 6 months was significantly lower in the two sirolimus groups (2mg 18.7%, $p = 0.002$; 5mg 16.8%, $p < 0.001$) than in the azathioprine group (32.3%); and the frequency of biopsy-confirmed acute rejection episodes was also lower (2mg 16.9%, $p = 0.002$; 5mg 12.0%, $p < 0.001$; azathioprine 29.8%). At 12 months, survival was similar in all groups for patients (97.2, 96.0 and 98.1% with sirolimus 2mg, 5mg and azathioprine, respectively) and grafts (94.7, 92.7 and 93.8% with sirolimus 2 mg, 5mg and azathioprine, respectively).

MacDonald et al.[33] also reported the excellent immunosuppressive effect of sirolimus in combination with cyclosporin. Five-hundred and sixty-six recipients of primary mismatched cadaveric or living donor renal allografts were randomly assigned in a 2:2:1 ratio to receive a daily dose of either 2mg or 5mg of sirolimus or to receive a matched placebo in addition to microemulsion cyclosporin and corticosteroids. The overall rate of the primary endpoint, which is a composite of the first occurrence of biopsy-confirmed acute rejection, graft loss or death, for the 6-month period after transplantation was 30.0% in the 2 mg/day sirolimus group and 25.6% (56/219) in the 5 mg/day sirolimus group, and this was significantly lower than the 47.7% (62/130) in the placebo group ($p = 0.002$, $p < 0.001$, respectively). The incidence of biopsy-confirmed acute rejection was 24.7% (56/227) in the sirolimus 2 mg/day group and 19.2% (42/219) in the 5 mg/day group, compared with 41.5% (54/130) in the placebo group ($p = 0.003$, $p < 0.001$, respectively), representing a significant reduction in acute rejection.[33] In this report, the incidence of hypercholesterolaemia, hyperlipidaemia or thrombocytopenia was significantly more frequent in the sirolimus groups than the placebo group.

These two large scale, randomised studies clearly showed that sirolimus in combination with cyclosporin is much more potent than azathioprine in renal transplantation.

Since the combination of cyclosporin (or tacrolimus) and MMF has been widely employed in many transplant centres, randomised clinical trials between cyclosporin plus sirolimus and cyclosporin plus MMF will be helpful for understanding the

immunosuppressive potency and adverse events of sirolimus in combination with calcineurin inhibitors.[34] However, the incidence of biopsy-proven rejection observed in these clinical trials of sirolimus plus cyclosporin seems to be similar to that seen under cyclosporin plus MMF immunosuppression.

On the other hand, very limited experience is available on the combination of sirolimus with tacrolimus, particularly after renal transplantation. Only one relatively large scale clinical study has been conducted, by Hricik et al.,[35] and they used the combination of sirolimus, tacrolimus and corticosteroids for maintenance immunosuppression in 56 African American kidney transplant recipients. The outcomes are compared with those of a concurrent control group consisting of 65 Caucasian primary kidney transplant recipients whose maintenance immunosuppression consisted of MMF, tacrolimus and corticosteroids. The incidence of acute rejection in the first 3 months posttransplantation was 7.1% in African Americans and 16.9% in Caucasians (not statistically significant). Actuarial 2-year patient (97 and 89%, in African American and Caucasians, respectively), graft (89 and 85%, respectively), and rejection rates (17.9 and 18.5%, respectively) were equivalent in the two groups. Although African American renal transplant recipients generally are categorised as a group of patients at high risk for acute and chronic rejection of their allograft and usually show poor outcomes, the combination of sirolimus, tacrolimus and corticosteroids was proven to be effective in reducing rejection episodes in this study.[35]

Other than the above report, no other study comparing sirolimus plus tacrolimus and MMF plus tacrolimus immunosuppression has been reported in the literature. According to this data, the combination of sirolimus and tacrolimus seems to be more potent than MMF plus tacrolimus immunosuppression since the two regimens showed almost the same incidence of rejection episodes even though the sirolimus group contained more high risk patients than the MMF group. However, we cannot draw definitive conclusions on the superiority of sirolimus plus tacrolimus immunosuppression because data concerning this issue are still very limited.

5. Adverse Events

5.1 Infectious Complications

In a multicentre, randomised trial of tacrolimus plus MMF, tacrolimus plus azathioprine, and cyclosporin microemulsion plus MMF, there were no significant differences across the three treatment groups in opportunistic infections through to 6-months post-transplantation.[6] The European Tacrolimus versus Ciclosporin Microemulsion Renal Transplantation Study Group also reported that the observed frequency and type of infections were similar in the two treatment groups throughout the study. Namely, urinary tract infection was the most frequently reported (tacrolimus 28.3%; cyclosporin microemulsion 26.2%), and CMV infection was the most frequently recorded serious infection (tacrolimus 7%; cyclosporin microemulsion 6.3%).[9] Mayer et al.[5] also reported that the overall incidence of infection was comparable for patients receiving tacrolimus (75.6%) and cyclosporin (75.2%). The same tendency was also observed in patients treated with sirolimus.[30-35]

5.2 Nephrotoxicity

It is well known that cyclosporin-associated nephrotoxicity is the major obstacle in long-term cyclosporin-based immunosuppression, and we have shown that chronic cyclosporin-induced arteriolopathy could be responsible for at least part of the late kidney graft losses.[36] No difference in renal function was seen between the cyclosporin-treated and the tacrolimus-treated patients in the US and European trials.[5,19] Mihatsch et al.[37] concluded that nephrotoxicity seems to be as common in patients treated with tacrolimus as in those treated with cyclosporin. A review of the protocol biopsies at 2 years in the US multicentre trial also did not reveal any difference between the two groups.[38]

On the other hand, calcineurin inhibitor free clinical trials were performed with sirolimus immuno-

suppression. Flechner et al.[30] conducted a randomised, prospective trial of calcineurin inhibitor drug avoidance in 61 adult primary kidney transplant recipients. Thirty-one patients received sirolimus 5 mg/day and 30 patients received cyclosporin. The 1-year patient survival, graft survival and biopsy-confirmed acute rejection rates were not significantly different between the sirolimus-treated patients (96.7, 96.7 and 6.4%, respectively) and the cyclosporin-treated patients (100, 95.4 and16.6%, respectively). At 6 and 12 months, respectively, the sirolimus-treated patients showed significantly better ($p = 0.008$ and $p = 0.004$) mean serum creatinine levels (1.29 and 1.32 mg/dL) than the cyclosporin-treated patients (1.74 and 1.78 mg/dL, respectively).[30]

Johnson et al.[39] conducted an open-label study which evaluated cyclosporin withdrawal under sirolimus immunosuppression in renal transplantation. Upon enrolment, 525 renal transplant recipients received sirolimus 2mg, cyclosporin microemulsion and corticosteroids. At about 3 months, eligible patients were randomised (1 : 1) to remain on this regimen or to have the cyclosporin withdrawn and therapy continued with just sirolimus plus corticosteroids. At 12 months, overall graft and patient survival rates were 89.1 and 94.9%, respectively. In the 430 (82%) randomised patients, there was no difference in graft survival (95.8% cyclosporin vs 97.2% no cyclosporin) or patient survival (97.2 vs 98.1%, respectively). The incidence of biopsy-confirmed primary acute rejection was 13.1% during the pre-randomisation period. After randomisation, the acute rejection was 4.2% and 9.8% for cyclosporin and no cyclosporin, respectively ($p = 0.035$). These investigators concluded that administration of sirolimus, cyclosporin and corticosteroids for 3 months post-transplant, followed by elimination of cyclosporin, is a safely used and effective alternative to continuous therapy with sirolimus, cyclosporin and corticosteroids that can result in better renal function and lower blood pressure.[39]

Since these studies show the usefulness and safety of calcineurin inhibitor elimination under sirolimus immunosuppression, calcineurin inhibitor elimination could be a possible choice of immunosuppression, especially for patients with calcineurin-associated nephrotoxicity. However, we need to observe the long-term outcomes of renal transplant recipients receiving a calcineurin inhibitor-free regimen under sirolimus immunosuppression. At this moment, such long-term data is not available. Furthermore, adverse effects of sirolimus, such as hypercholesterolaemia, hyperlipidaemia and thrombocytopenia should be carefully followed up. In my opinion, calcineurin inhibitor avoidance under sirolimus immunosuppression is promising; however, because of a lack of long-term data, we cannot draw a definitive conclusion at this time.

5.3 Hyperlipidaemia

It is well accepted that cardiovascular or cerebrovascular diseases are the main cause of death in renal transplant recipients. Attention must be paid to the cardiovascular risk profile during post-transplant follow-up.[40] Arterial hypertension and hyperlipidaemia are well known adverse effects of cyclosporin. Since the original publication of the two randomised trials,[5,19] the long-term safety profiles of both calcineurin inhibitors have been reported. The 3-year outcome of the US trial[21] showed significantly lower levels of serum cholesterol, triglycerides and low-density lipoprotein (LDL) cholesterol (198.9 vs 226.3 mg/dL, 158.5 vs 193.4 mg/dL and 116.7 vs 138.7 mg/dL, respectively) in the tacrolimus-treated patients than the cyclosporin-treated patients. The European trial demonstrated similar results;[41] namely, tacrolimus-treated patients had significantly lower cholesterol and LDL cholesterol levels 1 year after transplantation, although triglyceride levels were not significantly different between the two groups. Several studies have shown that conversion from cyclosporin to tacrolimus causes a significant decrease in serum lipids.[42,43] In all of the above-mentioned studies,[21,41-43] a lower systemic blood pressure was also noted in the tacrolimus-treated patients.

A randomised, three-arm (tacrolimus plus azathioprine, tacrolimus plus MMF, cyclosporin microemulsion plus MMF), open-label, prospective study

was performed in the US. Lipid profiles were measured in each patient through to 6-months post-transplant. There were significantly greater elevations from baseline in total and LDL cholesterol in the cyclosporin microemulsion plus MMF group compared with either of the tacrolimus groups. Although there was no difference in the percentage of patients treated for hyperlipidaemia at the time of transplantation, a greater percentage of patients were receiving lipid-lowering agents in the cyclosporin microemulsion group at 6-months post-transplant.[6] The European Tacrolimus versus Cyclosporin Microemulsion Renal Transplantation Study Group also showed a significantly lower incidence of hypercholesterolaemia in tacrolimus-treated recipients than in cyclosporin-microemulsion-treated recipients.[9]

Manu et al.[44] compared the incidence and severity of hyperlipidaemia between cyclosporin-treated and tacrolimus-treated Japanese recipients. Average total cholesterol levels at 1 year after transplantation were 227 ± 55 mg/dL and 193 ± 38 mg/dL in the cyclosporin- and tacrolimus-treated recipients, respectively. Triglyceride levels were also significantly lower in the tacrolimus-treated patients than in the cyclosporin-treated recipients (136 ± 77 in the tacrolimus group, 183 ± 99mg/dL in the cyclosporin group). Tacrolimus-treated recipients showed significantly lower levels of triglyceride and total cholesterol compared with the cyclosporin-treated recipients, whereas there was no significant difference in high density lipoprotein cholesterol levels between the two groups.[44] These data clearly show that even in Asian renal allograft recipients who have a low dietary fat intake, the lipid levels are much lower in tacrolimus-treated recipients than in cyclosporin-treated patients. These improved lipid profiles, found in tacrolimus-treated recipients may contribute to a better long-term outcome.

5.4 Diabetogenicity

The diabetogenic effect of calcineurin inhibitors is well documented in many reports, as reviewed by Weir and Fink.[45] For tacrolimus, the results of experimental studies suggest pancreatic islet cell toxicity with diminished insulin secretion, as with cyclosporin.[46]

Post-transplant diabetes mellitus (PTDM) is a major adverse effect of immunosuppressive agents, such as corticosteroids and calcineurin inhibitors. It is well recognised that corticosteroids cause PTDM primarily in a dose-dependent manner by inducing insulin resistance. Also, it is well known that calcineurin inhibitors, such as cyclosporin and tacrolimus, cause PTDM. For cyclosporin, the diabetogenic actions seemed to involve a reduction in pancreatic β-cell volume, which was caused by inhibition of both DNA and mRNA synthesis. Tacrolimus caused morphological damage to β cells and impaired insulin synthesis and secretion.[46]

Risk factors for the development of PTDM with tacrolimus therapy are the tacrolimus dose and trough blood concentrations, the concomitant use of high doses of corticosteroids, advanced age of the recipients, race, and the existence of pre-transplant prediabetes and obesity. A subgroup analysis of the US trial results[47] demonstrated that, in particular, African Americans are at risk for PTDM: 36.6% developed diabetes at 12 months versus 12.2% of the Caucasian Americans. In a recent study by van Hooff et al.,[48] early post-transplant glucose metabolism was compared in renal transplant patients treated with low-dose tacrolimus or with cyclosporin. Only one cyclosporin-treated patient developed diabetes. No differences were seen in the glucose metabolism between the two treatment groups. These data clearly demonstrated that the diabetogenic effect of tacrolimus is indeed dose-dependent and that by maintaining lower trough levels as well as using low doses of corticosteroids, the risk of *de novo* diabetes is minimal. Our data also showed that the incidence of insulin-dependent PTDM in tacrolimus-treated patients is comparable with that of cyclosporin-treated individuals.[49]

In the previously discussed US controlled trial, the incidence of PTDM was as high as 19.9% in the tacrolimus-treated patients versus 4% in the cyclosporin group, and in the European trial the incidences were 11.6 and 2.1%, respectively.[5,19] One-

third of the tacrolimus-treated patients with PTDM were insulin-free.

Recently, a randomised, three-arm (tacrolimus plus azathioprine, tacrolimus plus MMF, cyclosporin microemulsion plus MMF), open-label, prospective study showed that the incidence of new onset PTDM was identical in the cyclosporin microemulsion plus MMF and tacrolimus plus MMF treatment groups (6.5%), and was higher in the tacrolimus plus azathioprine group (12.3%).[6]

Squifflet et al.[8] reported that the incidence of PTDM, which was defined as the sustained need for insulin therapy in previously nondiabetic patients, was 3% (6 of 200 patients) and, thus, remarkably low without significant differences between the treatment groups (3.0, 6.3 and 0% in tacrolimus + methylprednisolone [MP] + MMF 1g, tacrolimus + MP + MMF 2g, and tacrolimus + MP, respectively). These authors concluded that the improved safety profile could probably be attributed to the low dosage and target trough tacrolimus concentrations.[8] Margreiter et al.[9] also conducted a large, randomised, multicentre study comparing tacrolimus and cyclosporin microemulsion, and reported no significant difference in the incidence of PTDM between the two treatments (4.5% with tacrolimus vs 2.0% with cyclosporin microemulsion; $p = 0.105$).

Although in early clinical trials of tacrolimus, a significantly higher incidence of PTDM was reported in tacrolimus-treated patients than in cyclosporin-treated recipients, the incidence of PTDM under tacrolimus immunosuppression has become less frequent in recent randomised trials comparing tacrolimus and cyclosporin microemulsion (see table I). Both reduction of corticosteroid dosage and the low target trough tacrolimus concentrations seem to contribute to the recent marked reduction of the incidence of PTDM under tacrolimus immunosuppression.

5.5 Malignancy

Mayer et al.[5] conducted a multicentre, randomised trial comparing tacrolimus and cyclosporin, and reported that malignancies were diagnosed in 1.0% (3/303) of the patients receiving tacrolimus and in 1.4% (2/145) of the cyclosporin treatment group. In addition, Margreiter et al.[9] did not find any differences in the incidence of malignancies between tacrolimus- and cyclosporin microemulsion-treated recipients. Thus, recent large, randomised studies could not show any differences in the incidence of malignancy between patients treated with tacrolimus or cyclosporin.

5.6 Other Adverse Events

In a multicentre, randomised study, Pirsch et al.[19] reported that the incidence of tremor, which is a well known adverse effect of calcineurin inhibitors, was significantly greater in patients receiving tacrolimus than it was for those receiving cyclosporin (tacrolimus 54.1% vs cyclosporin 33.8%). However, the incidences of hirsutism, gingivitis and gum hyperplasia were significantly lower in the tacrolimus-treated recipients than in those receiving cyclosporin.[19] Mayer et al.[5] also reported that tremor occurred significantly more frequently in the tacrolimus treatment group (tacrolimus 34.7% vs cyclosporin 11.7%). However acne, gingival hyperplasia and hirsutism were reported significantly less frequently in the tacrolimus treatment group. Margreiter et al.[9] also reported that gum hyperplasia and hirsutism were significantly more common in the cyclosporin microemulsion group than in the tacrolimus group and, conversely, tremor was more frequent in the tacrolimus group. Thus, tremor is consistently more common with tacrolimus, and hirsutism and gum disease more common with cyclosporin.

6. Steroid-Sparing Effects

Corticosteroids have played an important role in the development of successful organ transplantation.[20] However, the adverse effects of corticosteroids include hypertension, hyperlipidaemia, accelerated atherosclerosis, osteopenia, avascular necrosis of the joints, cataracts, weight gain and steroid-induced diabetes. Cardiovascular disease is a major cause of post-transplant mortality and morbidity. Steroid-associated hypertension, hyperlipidaemia, glucose intolerance and diabetes play an important

role in the pathogenesis of atherosclerosis. Furthermore, cataracts may occur early in the post-transplant period.[50] Since steroid-associated adverse events occur in the early post-transplant period, early withdrawal of corticosteroids is likely to be of more benefit to transplant recipients than late withdrawal.

Tarantino et al.[51] reported the results of cyclosporin monotherapy and showed that it was possible to perform transplants without the use of corticosteroids. However, it was only possible to maintain 30–50% of the patients off corticosteroids in the long-term. Corticosteroid withdrawal has been associated with an increased incidence of acute rejection in almost all reported studies.[20] Ponticelli[52] reported that about 30% of patients who were taken off corticosteroids experienced acute rejection. Hricik et al.[53] withdrew corticosteroids rapidly in the few weeks after transplantation in patients receiving cyclosporin-based treatment and 60% of the recipients experienced rejection, which was often severe and steroid-resistant.

Montagnino and colleagues[54] conducted a randomised, controlled trial which included 354 cadaveric renal transplant recipients. The patients were assigned to receive either cyclosporin monotherapy, cyclosporin plus corticosteroids, or cyclosporin plus corticosteroids and azathioprine. Intention-to-treat analysis showed that 9-year actuarial patient and graft survival were 94.0 and 73.3%, respectively, with monotherapy, 87.3 and 65.9% with dual therapy, and 87 and 72.2% with the triple therapy. The incidence of acute rejection was 69.5, 49.5, 49.2%, respectively, with cyclosporin monotherapy, dual therapy and triple therapy. Patients receiving cyclosporin monotherapy showed a significantly higher incidence of acute rejection than those in the other two groups. However, actuarial patient and graft survival did not differ among the three treatment arms. Monotherapy was associated with a lower incidence of extra renal complications, such as cataracts, osteoporosis and cardiovascular complications than the other two groups. This study showed a lack of corticosteroids in the immunosuppression regimen does not affect the long-term outcomes of renal transplantation.[55]

However, since many well-designed reports of steroid withdrawal are not available at this moment, we should be careful to draw definitive conclusions about the safety of steroid withdrawal in renal transplantation.

Since tacrolimus exerts a much more potent immunosuppressive effect than cyclosporin, steroid withdrawal seems to be safer in tacrolimus-based than in cyclosporin-based immunosuppression. The Pittsburgh group has reported the largest series of recipients undergoing steroid withdrawal under tacrolimus immunosuppression. They have reported on steroid withdrawal in both adult and paediatric patients, which was achieved in some 70% of successfully transplanted patients. The 3-year actuarial patient and graft survival rates in adults withdrawn from corticosteroids were 98 and 94%, respectively, and in those still receiving corticosteroids (a group with more rejection, a higher rate of delayed graft function and older mean donor age), they were 80 and 50%, respectively.[56] In paediatric patients, over 90% of the patients were withdrawn from corticosteroids, and long-term steroid withdrawal was feasible in 70%.[57] Five-year patient and graft survival rates in paediatric patients taken off corticosteroids were 96 and 82%, respectively.

Fifty-two patients from the University of Chicago underwent steroid withdrawal 1 week after transplantation under tacrolimus plus MMF immunosuppression with basiliximab induction.[58,59] Patient and graft survival rates were 100 and 96%, respectively. The incidence of rejection was 25% and long-term steroid withdrawal was obtained in 76% of the patients.

On the other hand, Mahalati et al.[59] conducted a single-centre, open-label pilot study which examined the long-term success of steroid withdrawal from a cyclosporin plus sirolimus regimen in 156 renal transplant recipients. They reported that at 3 years, 117 patients (75%) had been successfully withdrawn from corticosteroids. During the 3 years, acute rejection episodes occurred in 6.4% and chronic rejection in 5.1% of the patients. They con-

cluded that steroid-free treatment under sirolimus immunosuppression can be safely used. In addition, Swanson et al.[60] examined the effectiveness of sirolimus monotherapy in 12 renal transplant patients. After renal transplantation, the recipients received rabbit antithymocyte globulin in the induction and sirolimus monotherapy. They showed that monotherapy immunosuppression with sirolimus can successfully prevent acute rejection (25% [3/12] had an acute rejection episode). According to these data, it seems that steroid-free immunosuppression with sirolimus can be safely used. However, once again, the available data is very limited and future clinical trials of steroid-free regimens with sirolimus are needed to confirm these data.

7. Conclusions

Overall, short-term patient and graft survival with cyclosporin microemulsion and tacrolimus is almost identical. The incidence of acute rejection is generally lower with tacrolimus than with cyclosporin in patients treated concomitantly with azathioprine. However in conjunction with MMF, the difference in the incidence of acute rejection between tacrolimus and cyclosporin became smaller than in the pre-MMF era. Adverse events, such as hypertension, hyperlipidaemia and cosmetic changes (gum hypertrophy, hirsutism) seem to be less frequent in tacrolimus-treated than in cyclosporin-treated patients. Recent randomised studies have shown that the incidence of PTDM was almost identical between low-dose tacrolimus- and cyclosporin-treated patients (table I).

According to the data discussed in this review, the recommendation from our kidney centre in the choice of calcineurin inhibitors at this moment is that either cyclosporin or tacrolimus can be used safely and effectively for patients without any risk factors. However, we prefer tacrolimus to cyclosporin in patients with a high risk for rejection, such as those with ABO-incompatibility, delayed graft function, sensitisation and African American race, and some other risk factors, such as hypertension and hyperlipidaemia. Moreover, tacrolimus may be preferable to cyclosporin for women because of hirsutism and for children because of the steroid-sparing effect. We consider that cyclosporin should be chosen when patients experience tacrolimus-related adverse events, such as severe chest pain, tremor, gastrointestinal symptoms and encephalopathy.

In conclusion, well tolerated and effective immunosuppression is feasible with both cyclosporin and tacrolimus. As the study of new immunosuppressive agents continues, we may be able to eliminate calcineurin inhibitors in the future. However, in the current immunosuppressive regimen, a calcineurin inhibitor, either tacrolimus or cyclosporin, is the essential basic standard immunosuppressant. Clinicians need to decide the best means of optimising therapy for individual patients, based on various risk factors, such as risk of rejection, i.e. sensitisation, delayed graft function and ABO-incompatibility, and some adverse events, such as hypertension, hyperlipidaemia and cosmetic changes.

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