Impact of Tacrolimus and Mycophenolate Mofetil Combination on Cardiovascular Risk Profile after Kidney Transplantation

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Cardiovascular risk factors after kidney transplantation are enhanced as a result of the chronic use of immunosuppressants. Tacrolimus with mycophenolate mofetil has become the most commonly used combination after kidney transplantation. Cardiovascular risk factors that are related to the use of this combined therapy have been analyzed in various clinical trials in comparison with other immunosuppressive therapies. This review summarizes the main results of these studies regarding arterial hypertension, lipid profile, posttransplantation diabetes, renal function, and even acute rejection rate. The aim is to characterize the cardiovascular risk profile of tacrolimus and mycophenolate mofetil association when compared with older and newer immunosuppressive associations.

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Cardiovascular risk factors after kidney transplantation are involved with the main causes of graft loss in the long term (1,2). First, they are important determinants of death with a functioning graft, because cardiovascular disease is an important cause of morbidity and the first cause of mortality in recipients of a kidney transplant. Second, many of these factors have been involved in the pathogenesis of chronic allograft nephropathy (CAN) (3). The cardiovascular burden that already is present at the moment of transplantation is greatly enhanced because of the chronic use of immunosuppressants.

Tacrolimus has become the most commonly used calcineurin inhibitor after kidney transplantation in the United States (4) and in many European countries. When compared with cyclosporine (CsA), tacrolimus seems to be related to a better blood pressure (BP) and lipid profile control (5–8). Besides, several comparative and conversion studies that were performed in kidney transplantation demonstrated that renal function may be better under tacrolimus treatment (5,7). This also was observed in studies on other solid-organ recipients (9) and even in healthy volunteers (10), suggesting that nephrotoxicity may be lower with tacrolimus. On the contrary, posttransplantation diabetes (PTD) may be considered the Achilles' tendon of tacrolimus with a greater incidence with tacrolimus than with CsA (11,12). Some authors have identified acute rejection also as a cardiovascular risk factor (13). Comparative trials that were performed with tacrolimus *versus* CsA in kidney transplantation have shown repeatedly that acute rejection rates are lower with the former (11,12).

Mofetil mycophenolate (MMF) has been incorporated into the majority of the immunosuppressive combinations that are used in kidney transplantation (4), substantially decreasing the acute rejection rates. MMF does not exhibit a negative impact on BP, lipid profile, or glycemic metabolism (14), and MMF is not nephrotoxic. MMF progressively has become the most common adjunctive immunosuppressant for tacrolimus (4), and it probably has changed the cardiovascular profile of this calcineurin inhibitor. In the present article, we review the cardiovascular risk properties of this immunosuppressive combination in comparison with other tacrolimus-based therapies, either in combination with a classical partner, azathioprine, or with mammalian target of rapamycin (mTOR) inhibitors, basically sirolimus, because data on its association with everolimus are not available. Also, we reviewed the scarce bibliography on the comparison of tacrolimus/MMF combination with calcineurin inhibitor-free therapies and also with CsA/MMF association. Main data are presented in Tables 1 and 2. To perform this review, we exclusively analyzed prospective and randomized clinical trials that included at least one arm with tacrolimus and MMF combination. Classical cardiovascular risk factors as well as renal function and acute rejection were the specific variables tested in the present review.

Impact of Tacrolimus-MMF on Cardiovascular Risk Factors after Kidney Transplantation

Arterial Hypertension

Tacrolimus/MMF association has not offered apparent advantages on BP control in comparison with dual therapy or triple therapy with steroids/tacrolimus/azathioprine or steroids/CsA/MMF, although detailed data are not available in several studies (15–19). However, tacrolimus/MMF combination has been tested as a steroid-sparing strategy after kidney transplantation in selected low-risk patients. Withdrawal of

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Table 1. Cardiovascular risk factors as described in main clinical trials including at least one group of patients treated with tacrolimus/MMF combination[a]

Study	Tested Therapy	Follow-Up	Arterial Hypertension	Hyperlipidemia	PTD	Renal Function	Acute Rejection
			Adverse Event		*De novo* Insulin Therapy >30 D	SCr	Kaplan-Meier (Clinically Suspected)
Squifflet *et al.* (15)	Tac + CS (n = 82)	6 mo	32.8%	NA	0	157 μmol/L ± 68 μmol/L	48.5%[b]
	Tac + CS + MMF 1 g/d (n = 79)	6 mo	32.8%	NA	3.0%	142 μmol/L ± 45 μmol/L	24.8%[b]
	Tac + CS + MMF 2 g/d (n = 71)	6 mo	32.8%	NA	6.3%	145 μmol/L ± 69 μmol/L	22.9%[b]
				Hyperlipidemia/Hypercholesterolemia (Adverse Event)		Increased Creatinine (Adverse Event)	Biopsy Proven
Miller *et al.* (16)	OKT3/ATGAM + Tac + Aza (n = 59)	1 yr	NA	16.9%/8.5%	19.0%[b]	40.7%	32.2%[b]
	OKT3/ATGAM + Tac + MMF 1 g/d (n = 59)	1 yr	NA	18.6%/8.5%	12.2%[b]	39.0%	32.2%[b]
	OKT3/ATGAM + Tac + MMF 2 g/d (n = 58)	1 yr	NA	19.0%/6.9%	4.7%[b]	25.9%	8.6%[b]
				6-Mo Data	*De novo* Insulin Therapy >30 D		Biopsy Proven
Gonwa *et al.* (19)	Antibody induction of DGF Tac + CS + Aza (n = 76)	3 yr	NA	Change from baseline in total cholesterol: +29.8[b] Change from baseline in LDL cholesterol: +21.1[b] % of patients with statins at 6 mo: 5.3%[b]	11/57 (19.3%)	SCr = 1.40 mg/dl % patients with SCr >1.5 mg/dl = 35.8% % patients with SCr >2.0 mg/dl = 18.9% CrCl = 62.3 ml/min	21.1%
	Antibody induction of DGF Tac + CS + MMF (n = 72)	3 yr	NA	Change from baseline in total cholesterol: +24.29[b] Change from baseline in LDL cholesterol: + 0.7[b] % of patients with statins at 6 mo: 12.5%[b]	6/46 (13.0%)	SCr = 1.40 mg/dl % patients with SCr >1.5 mg/dl=38.3% % patients with SCr >2.0 mg/dl=17.0% CrCl = 59.3 ml/min	16.7%
	Antibody induction of DGF CsA + CS + MMF (n = 75)	3 yr	NA	Change from baseline in total cholesterol: +56.24[b] Change from baseline in LDL cholesterol: +43.16[b] % of patients with statins at 6 mo: 26.7%[b]	3/46 (6.5%)	SCr = 1.60 mg/dl % patients with SCr >1.5 mg/dl = 51.0% % patients with SCr >2.0 mg/dl = 21.6% CrCl = 56.1 ml/min	25.3%
				Lipid-Lowering Medication Use at 3 yr	*De novo* Insulin at Any Time		Biopsy Proven
Pascual *et al.* (20)	Tac + MMF + CS (stop 3 mo) (n = 221)	3 yr	Use of antihypertensives: 61.3%[b] Mean number per patient: 1.8 SBP: 133.6 mmHg[b] DBP: 80.3 mmHg	16.6%[b]	6.7%	SCr = 126 μmol/L Estimated CrCl = 63 ml/min	16.7%
	Tac + MMF + CS (n = 225)	3 yr	Use of antihypertensives: 66.2%[b] Mean number per patient: 1.8 SBP: 136.2 mmHg[b] DBP: 79.2 mmHg	26.2%[b]	8%	SCr = 124.6 μmol/L Estimated CrCl = 61.9 ml/min	23.3%
	Tac + MMF + CS MMF (stop 3 mo) (n = 219)	3 yr	Use of antihypertensives: 74.4%[b] Mean number per patient: 2 SBP: 139.8 mmHg[b] DBP: 81.3 mmHg	28.1%[b]	7.6%	SCr = 130 mmol/L Estimated CrCl = 63 ml/min	15.7%
					De novo Insulin Therapy >30 D		Biopsy Proven
Rostaing *et al.* (21)	Dac/Tac/MMF (n = 260)	6 mo	Adverse event: 15.8% Use of antihypertensives: 51.4%	Change from baseline total cholesterol: −0.19 ± 1.29 mmol/L[b] Total cholesterol at 6 mo: 4.93 ± 1.12 mmol/L	0.4%[b]	SCr = 131.0 μmol/L Estimated CrCl = 52.0 ± 17.8 ml/min	16.5%
	Tac/MMF/CS (n = 278)	6 mo	Adverse event: 15.1% Use of antihypertensives: 61.5%	Change from baseline in total cholesterol: +0.19 ± 1.33 mmol/L[b] Total cholesterol at 6 mo: 5.25 ±1.24 mmol/L	5.4%[b]	SCr = 125.0 μmol/L Estimated CrCl = 53.6 ± 17.8 ml/min	16.5%

Table 1. Continued[a]

Study	Tested Therapy	Follow-Up	Arterial Hypertension	Hyperlipidemia	PTD	Renal Function	Acute Rejection
			Adverse Event		*De novo* Insulin Therapy >30 D	SCr	Kaplan-Meier (Clinically Suspected)
			New Onset or Worsening				Biopsy Proven
Vitko *et al.* (23)	Tac + CS + Srl 0.5 mg (n = 325)	6 mo	14.8%[b]	Hyperlipidemia/hypercholesterolemia (adverse event):19.4%/5.8%[b] Use of lipid-lowering drugs: 29.8%[b]	*De novo* diabetes (adverse event): 6.8%[b] *De novo* diabetes requiring insulin: 2.7%	SCr = 130.0 μmol/L Estimated CrCl = 51.7 ml/min	25.2%
	Tac + CS + Srl 2 mg (n = 325)	6 mo	15.4%[b]	Hyperlipidemia/hypercholesterolemia (adverse event): 24%/13.2%[b] Use of lipid-lowering drugs: 22.2%[b]	*De novo* diabetes (adverse event): 15.2%[b] *De novo* diabetes requiring insulin: 5.2%	SCr = 132.6 μmol/L Estimated CrCl = 49.5 ml/min	15.7%
	Tac + CS + MMF (n = 327)	6 mo	9.2%[b]	Hyperlipidemia/hypercholesterolemia (adverse event): 11.0%/5.5%[b] Use of lipid-lowering drugs: 17.4%[b]	*De novo* diabetes (adverse event): 9.5%[b] *De novo* diabetes requiring insulin: 5.4%	SCr = 131.0 μmol/L Estimated CrCl = 52.5 ml/min	22.3%
			Results at 6 mo		*De novo* Insulin Therapy >30 D		Biopsy Proven
Mendez *et al.* (25)	Antibody induction of DGF; Tac + CS + Srl (n = 185)	1 yr	SBP: 134 ± 18[b] DBP: 80 ± 11[b]	Hyperlipidemia (adverse event): 89%[b] Total cholesterol >240 mg/dl: 29.3%[b] Triglycerides >200 mg/dl: 55.6%[b] Use of lipid-lowering drugs: 42%[b]	8%	SCr = 1.5 mg/dl[b] % patients with SCr >1.5 mg/dl = 45.4% % patients with SCr >2. 0 mg/dl = 20.4%[b] CrCl = 54.3 ml/min % patients with CrCl ≤60 ml/min = 66.2[b]	13.0%
	Antibody induction of DGF; Tac + CS + MMF (n = 176)	1 yr	SBP: 130 ± 19[b] DBP: 77 ± 11[b]	Hyperlipidemia (adverse event): 72%[b] Total cholesterol >240 mg/dl: 12.2%[b] Triglycerides >200 mg/dl: 38%[b] Use of lipid-lowering drugs: 22%[b]	8%	SCr = 1.3 mg/dl[b] % patients with SCr >1.5 mg/dl = 35.7% % patients with SCr >2.0 mg/dl = 11.0%[b] CrCl = 58.4 ml/min % patients with CrCl ≤60 ml/min = 53.9[b]	11.4%
					De novo PTD		Biopsy Proven
Ciancio *et al.* (26)	Dac + CS + Tac + Srl (n = 50)	1 yr	NA	Total cholesterol: 202 ± 39 mg/dl Triglycerides: 163 ± 1.9 Use of lipid-lowering drugs: 54%[b]	17%[b]	SCr = 1.4 ± 1.3 mg/dl CrCl = 73 ± 25 ml/min	4.0%
	Dac + CS + Tac + MMF (n = 50)	1 yr	NA	Total cholesterol: 193 ± 52 mg/dl Triglycerides: 151 ± 1.6 Use of lipid-lowering drugs: 16%[b]	14%[b]	SCr = 1.2 ± 1.4 mg/dl CrCl = 84 ± 39 ml/min	4.0%
	Dac + CS + CsA + Srl (n = 50)	1 yr	NA	Total cholesterol: 201 ± 39 mg/dl Triglycerides: 187 ± 1.7 Use of lipid-lowering drugs: 80%[b]	33%[b]	SCr = 1.5 ± 1.5 mg/dl CrCl = 71 ± 28 ml/min	14.0%
			12-Mo Data	12-Mo Data	Iothalamate Clearance	Biopsy Proven and with Protocol Biopsies	Biopsy Proven
Larson *et al.* (24)	Thym + CS + Tac + MMF	33 mo	SBP: 135 ± 22 mmHg DBP: 77 ± 14 mmHg Use of antihypertensives: 34%, 0; 47%, 1; 19%, 2 or more	Total cholesterol: 200 ± 33 mg/dl[b] Triglycerides: 174 ± 102 mg/dl[b] Use of lipid-lowering drugs: 36%[b]	10%	Mo 1: 62 ± 18 ml/min per 1.73 m^{2b} Mo 12: 55 ± 17 mL/min per 1.73 m^2 Mo 24: 55 ± 14 ml/min per 1.73 m^2 Change mo 1 to mo 12: −0.3 ml/min per 1.73 m^2 (NS mo 1 *versus* mo 12)	14%
	Thym + CS + Srl + MMF	33 mo	SBP: 137 ± 15 mmHg DBP: 77 ± 10 mmHg Use of antihypertensives: 21%, 0; 54%, 1; 25%, 2 or more	Total cholesterol: 219 ± 53 mg/dl[b] Triglycerides: 246 ± 131 mg/dl[b] Use of lipid-lowering drugs: 78%[b]	7.5%	Mo 1: 56 ± 16 ml/min per 1.73 m^{2b} Mo 12: 56 ± 16 ml/min per 1.73 m^2 Mo 24: 55 ± 16 ml/min per 1.73 m^2 Change mo 1 to mo 12: −5.7 ml/min per 1.73 m^2 (P = 0.01 mo 1 *versus* mo 12)	19%

[a]Aza, azathioprine; CrCl, creatinine clearance; CS, corticosteroids; CsA, cyclosporine; Dac, daclizumab; DBP, diastolic BP; DGF, delayed graft function; MMF, mycophenolate mofetil; NA, not available; PTD, posttransplantation diabetes; SP, systolic BP; SCr, serum creatinine; Srl, sirolimus; Tac, tacrolimus; Thym, Thymoglobulin. [b]$P < 0.05$ in comparisons between/among study groups.

Table 2. Impact of different immunosuppressive combinations on cardiovascular risk factors with steroids/tacrolimus/MMF as the reference[a]

	St/Tac/MMF	St/Tac ± Aza	Tac/MMF	St/Tac/Srl	St/CsA/MMF	St/MMF/Srl
Arterial hypertension	Ref	=	Better	Worse	=	=
Hyperlipidemia	Ref	=	Better	Worse	Worse	Worse
PTD	Ref	Worse	Better	= or worse	Better	=
Renal function	Ref	= or worse	=	Worse	Worse	=
Acute rejection	Ref	Worse	=	= or better	Worse	=

[a]Conclusions of the authors on randomized clinical trials used for this review. Induction with antilymphocyte antibodies has not been specified. Ref, reference group, St, steroids.

steroids at 3 mo after renal transplantation was possible with a low incidence of acute rejection and similar efficacy outcomes after 3 yr than those that were observed with standard triple therapy (20). Withdrawal of steroids was related to a lower systolic BP and a lower need for antihypertensive medications. Whereas 60.6% of patients in whom steroids had been withdrawn were taking antihypertensive medication, 67 and 71.6% of patients who were under triple therapy with steroids/tacrolimus/MMF and with steroids/tacrolimus, respectively, were receiving such treatment at 3 yr after transplantation. Tacrolimus/MMF also has been used with no steroids by induction with daclizumab (21). The regimen demonstrated similar efficacy outcomes than standard triple therapy and again a trend toward a better BP control. Indeed, at 6 mo after transplantation, whereas 51.4% of the patients who were on daclizumab/tacrolimus/MMF were receiving antihypertensive medications, 61.5% of the patients were being treated for arterial hypertension in the standard arm.

Some studies that compared tacrolimus/MMF with the newer combination tacrolimus/sirolimus described direct or indirect data of a better BP control with the former, in parallel with the differences that were observed in renal function between the groups (22,23). A multicenter, American, randomized, clinical trial compared the outcome of kidney transplant patients who were receiving tacrolimus/sirolimus *versus* tacrolimus/MMF (22). At 6 mo after transplantation, lower diastolic BP values were observed in tacrolimus/MMF combination. In a similar way, a clinical trial that included >900 patients who were randomly assigned to receive tacrolimus/MMF *versus* tacrolimus/sirolimus 0.5 mg/d *versus* tacrolimus/sirolimus 2 mg/d observed that *de novo* hypertension or worsening of pretransplantation arterial hypertension was observed more frequently in both sirolimus groups (23).

A randomized, clinical trial that compared tacrolimus/MMF and MMF/sirolimus combination did not prove the expected differences favoring the latter in terms of BP control in the short term (24). At 12 mo after transplantation, no statistically significant differences were observed in systolic and diastolic BP or in the need for antihypertensive medications. The absence of a statistical advantage regarding BP control and even renal function in calcineurin inhibitor–free immunosuppression *versus* tacrolimus/MMF therapy in this interesting trial is provocative. This study included a great percentage of living donors and preemptive transplants. It remains to be demonstrated whether tacrolimus/MMF will offer a similar outcome regarding these variables when trials with less optimal kidneys are performed.

Hyperlipidemia

The addition of MMF to a tacrolimus-based immunosuppression with steroids and/or azathioprine seemed not to have been related to an improvement in lipid profile from available data, despite a reduction of acute rejection and therefore the need for bolus of corticosteroids (15,16). In fact, the reported incidences of hyperlipidemia and hypercholesterolemia were similar among patients who were receiving tacrolimus/azathioprine *versus* tacrolimus/MMF 1 g/d *versus* tacrolimus/MMF 2 g/d (16). However, the only available data referred to spontaneously reported adverse events, without a comparison of analytical parameters or concomitant medication, such as the use of statins.

In comparison with CsA/MMF, tacrolimus-based regimens in combination either with MMF or with azathioprine demonstrated a better outcome on serum lipids up to 6 mo after transplantation (17). Change in total cholesterol and LDL cholesterol from baseline to this time point was significantly lower in both tacrolimus regimens in comparison with CsA/MMF. Whereas the percentage of patients who were taking lipid-lowering medication at baseline was similar in the three groups, 26.7% of patients in the CsA/MMF group were receiving lipid-lowering medication at 6 mo *versus* 5.3% of patients in tacrolimus/azathioprine and 12.5% of patients in tacrolimus/MMF groups, this difference reaching statistical significance.

Tacrolimus in combination with MMF allowed the withdrawal of steroids 3 mo after transplantation, which resulted in a significant reduction in total and LDL cholesterol levels, this reduction being maintained up to 3 yr after transplantation (20). A similar finding was described in a trial that compared a standard regimen with steroids/tacrolimus/MMF *versus* tacrolimus/MMF combination with no steroids and daclizumab induction (21). Total cholesterol levels decreased from baseline to the sixth month after transplantation in the steroid-free arm, whereas it increased in the standard group. No differences were described for LDL or triglyceride levels. We may conclude that steroids have a significant impact in the evolution of serum lipids after transplantation. Tacrolimus in combination with MMF offers the possibility of safely avoiding or withdrawing corticosteroid therapy, which results in a better outcome of lipid profile.

The description of a worse lipid profile control and a more extended use of statins with tacrolimus in combination with sirolimus when compared with tacrolimus/MMF is consistent in the various trials that have compared both immunosuppressive combinations (23,25,26). Of note, tacrolimus/sirolimus combination was related to higher cholesterol and triglyceride levels than tacrolimus/MMF at different points after transplantation as well as to a more frequent need for lipid-lowering medication. However, tacrolimus/sirolimus seemed to offer a better lipid profile control than CsA/sirolimus combination (26). Although hyperlipidemia in fact is a widely known adverse effect of mTOR inhibitors (27), there is clinical evidence that mTOR inhibitors such as sirolimus reduce the incidence of graft vascular disease in human cardiac transplantation, despite inducing hyperlipidemia in these patients (28). Therefore, whether the effect of this hyperlipidemia is counterbalanced by the antiproliferative properties of these drugs remains to be elucidated. As expected, calcineurin inhibitor–free immunosuppression based on sirolimus/MMF combination offers also a greater incidence of hyperlipidemia when compared with tacrolimus in association with MMF (24).

PTD

The reported incidence of PTD in the first studies that evaluated tacrolimus/MMF (15,16) in comparison with classical combinations were lower than the ones described in the first trials that evaluated tacrolimus *versus* CsA (5,6). Even though possible reasons are the use of lower dosages and target trough levels of tacrolimus, the use of MMF may be an important cause also through different mechanisms. MMF reduces acute rejection rate after transplantation. Therefore, its use also is related to a lower need for bolus of corticosteroids, which should be reflected in a lower cumulative dosage of corticosteroids. Besides, MMF should allow a lower exposure to tacrolimus with benefits regarding glycemic control. In fact, in the American trial that compared tacrolimus/azathioprine and tacrolimus/MMF 1 g/d and tacrolimus/MMF 2 g/d, the incidence of *de novo* use of insulin for ≥30 d after transplantation in patients with no history of diabetes was 19, 12.2, and 4.7%, respectively, in each group at 1 yr, although the difference did not reach statistical significance (16).

During and at 3 yr after transplantation, the incidence of PTD was numerically higher among tacrolimus regimens whether combined with MMF or azathioprine compared with CsA/MMF association (19). However, the distance between tacrolimus and CsA regimens regarding PTD seemed to be shortened when MMF was used as concomitant immunosuppression with the former. In fact, although the incidence of PTD was not statistically significant between tacrolimus/MMF and tacrolimus/azathioprine combinations, there was a statistically significant difference between tacrolimus/azathioprine and CsA/MMF regarding this metabolic adverse event.

Tacrolimus/MMF combination was related to a numerically lower incidence of PTD when steroids were withdrawn 3 mo after transplantation (20). Total steroid avoidance with daclizumab induction showed a striking effect on PTD, with a 0.4% incidence in comparison with 5.4% in a standard combination of steroids/tacrolimus/MMF (21).

Regarding sirolimus, there are controversial data published on its impact of the drug on glucose metabolism when combined with tacrolimus. Whereas some studies have not described a difference in PTD incidence when comparing tacrolimus/sirolimus with tacrolimus/MMF (25,26), other studies have described a more frequent incidence of this complication with tacrolimus/sirolimus, especially with higher dosages of sirolimus (23). Finally, no apparent differences in glucose metabolism disorders have been described for tacrolimus/MMF *versus* sirolimus/MMF combination (24).

As a whole, the majority of the studies that are referred to here did not use a proper definition for PTD and may have underestimated the real incidence of this complication with the various immunosuppressive combinations. However, a progressive decrease in the incidence of PTD with tacrolimus-based therapies has been observed in the past few years (29). The use of lower dosages and exposure to tacrolimus may account for this evolution, but the use of MMF may have been crucial through its direct impact on acute rejection rate. A more flexible use of steroids with tacrolimus/MMF offers the possibility of an even greater decrease in this posttransplantation complication.

Renal Function

Renal function was assessed in the European multicenter study that compared three tacrolimus-based regimes with steroids and no other adjunctive immunosuppressant, 1 g/d MMF, or 2 g/d MMF (15). At 6 mo after kidney transplantation, no significant differences were found regarding serum creatinine. A similar trial that was performed in the United States did not provide results on renal function at 6 mo after transplantation (16). However, the adverse event defined as an increase in serum creatinine levels seemed to be lower in the group of patients who received tacrolimus in combination with 2 g/d MMF (25.9%) than in patients who were treated with azathioprine (40.7%) or 1 g/d MMF (39%), although this difference did not reach statistical significance. Again, a multicenter trial that tested tacrolimus/MMF *versus* tacrolimus/azathioprine *versus* CsA-microemulsion/MMF, did not show statistical differences between the two tacrolimus-treated groups regarding renal function (17–19). However, both groups exhibited a better renal function in terms of serum creatinine than the group of patients who received CsA-microemulsion/MMF. In fact, the proportion of patients with creatinine values >1.5 mg/dl was higher in this last group. Importantly, this difference in renal function was observed up to 3 yr after transplantation (19).

We may interpret from these trials that no clear advantage on renal function seems to have been achieved with the tacrolimus/MMF combination *versus* previous immunosuppressive associations, such as double therapy or triple therapy with steroids/tacrolimus/azathioprine. However, registry data have described a more favorable outcome in renal function in kidney transplant patients who were treated with tacrolimus and MMF, in comparison with other immunosuppressants (30). It is possible that MMF increases the immunologic protection of the

graft, allowing a better renal function. MMF has run in parallel with a progressive decrease in tacrolimus exposure, which seems to be reflected in a better renal function. Renal function seemed to be better with tacrolimus than with CsA/MMF combination, independent of whether tacrolimus was combined with MMF or azathioprine (17–19). This difference may reflect a lower nephrotoxicity of tacrolimus-based regimens but also may reflect a lower immunologic damage of the graft.

Tacrolimus/MMF has allowed withdrawal of steroids at 3 mo after transplantation, which has not been related to a decrease in kidney allograft function even after 3 yr of transplantation (20). In a similar way, total avoidance of steroids with daclizumab induction has given similar results in terms of renal function than the one obtained with a standard regimen based on steroids/tacrolimus/MMF (21).

It is interesting that several trials have evaluated renal function in patients who received tacrolimus/MMF *versus* tacrolimus/sirolimus combinations (22,23,25,26); renal function was decreased with the second association in some of these studies (22,25,26). The ability of sirolimus to increase nephrotoxicity of calcineurin inhibitors has been well described. A pharmacokinetic interaction between CsA and sirolimus seems to have been responsible for the presence of high dosages of CsA in the renal tissue, enhancing the toxicity of CsA at this level (31). Some animal studies suggested that nephrotoxicity that is caused by tacrolimus/sirolimus combination may be lower than the one observed with CsA/sirolimus (32). However, in the clinical setting, tacrolimus/sirolimus does not provide as good kidney function as the one observed with tacrolimus in association with MMF. Whether this is due to an overexposure to one or both of the drugs remains to be elucidated.

Finally, only one report has compared tacrolimus/MMF immunosuppression with a calcineurin inhibitor–free regimen based on sirolimus/MMF (24). Renal function, evaluated in terms of iothalamate clearance, was significantly lower in the tacrolimus/MMF group at 1 mo after transplantation. However, no differences in iothalamate clearance were observed in the subsequent assessments at 12 and even 24 mo after transplantation. Surprising, whereas iothalamate clearance significantly decreased from the first to the 12th month after transplantation among sirolimus-treated patients, renal function remained stable in tacrolimus-treated patients during the same period. From a histologic point of view, no differences were observed between both groups according to chronic Banff scores that were applied to protocol biopsies, but chronic vascular scores were significantly worse in the tacrolimus group. This finding could have a negative clinical impact in the long term, although this has not been demonstrated up to 2 yr. Of note, in this study, the majority of the transplants were performed with kidneys from living donors. It remains to be demonstrated whether similar findings are achieved when kidneys from cadaveric donors are used.

Acute Rejection

Tacrolimus/MMF combination offers numerically lower acute rejection rates compared with tacrolimus/steroids and CsA/MMF/steroids (15,16,19). Concerning the dosage of MMF, there are contradictory data. In the European trial, tacrolimus in combination with 1 g/d MMF showed a similar rate of acute rejection but a safer profile than tacrolimus combined with 2 g/d MMF (15). However, in the American trial, the acute rejection rate was lower with 2 g/d MMF, possibly indicating that more high-risk patients had been included in this study (16).

Tacrolimus/MMF combination has been compared with tacrolimus/sirolimus in three studies (23,25,26). In two of them, with or without induction with daclizumab, acute rejection rates were similar among patients with tacrolimus/sirolimus *versus* tacrolimus/MMF. Notably, in one of these studies, patients who were on tacrolimus/sirolimus and tacrolimus/MMF exhibited a lower acute rejection incidence compared with patients who were on CsA/sirolimus. In another European study, tacrolimus/MMF was compared with tacrolimus and two fixed dosages of sirolimus, 0.5 mg and 2 mg/d. In this trial, tacrolimus and sirolimus 2 mg/d was associated with a lower rate of acute rejection, but the safety profile was more favorable to tacrolimus/MMF (23). Direct comparison of tacrolimus/MMF and the non-nephrotoxic protocol tacrolimus/sirolimus with steroids and Thymoglobulin in patients, most of whom had living donors and preemptive transplantation, showed similar clinical and subclinical acute rejection rates with the two combinations (24).

Finally, tacrolimus/MMF combination is a safe therapy that allows steroid withdrawal without an important risk for acute rejection (20), and tacrolimus/MMF with daclizumab has been tested successfully in steroid-sparing regimens (21). In summary, tacrolimus/MMF is an efficacious immunosuppressive protocol that avoids clinical and subclinical acute rejection and also offers a good safety profile (33).

Conclusion

Tacrolimus/MMF is the most frequently used immunosuppressive combination in the United States and Spain. This regimen not only offers an adequate protection against clinical and subclinical acute rejection, but also it is depicted as a well-tolerated association. In fact, the percentage of patients who change to other combinations in the midterm is lower than with other immunosuppressive associations (4).

MMF seems to have modified the cardiovascular risk profile related to older tacrolimus regimens, such as double therapy with steroids/tacrolimus or triple therapy with steroids/tacrolimus/azathioprine, especially regarding PTD, probably as a result of a lower acute rejection rate and a lower exposure to tacrolimus. Tacrolimus/MMF regimen allows the withdrawal or avoidance of steroids in selected patients without a high immunologic risk. Steroid-sparing strategies with tacrolimus/MMF result in an important change in the cardiovascular risk scenario. In fact, advantages have been observed in lipid profile, arterial hypertension, and glucose metabolism disorders. When compared with CsA/MMF, tacrolimus/MMF seems to be related to a better lipid profile and a better renal function and shortened distances with CsA-based therapies regarding PTD to what

had been observed with tacrolimus/azathioprine. Tacrolimus/MMF offers better lipid profile, BP control, and renal function than tacrolimus/sirolimus combination, with doubts regarding possible differences in glucose metabolism. Finally, the only available trial that compared tacrolimus/MMF therapy with calcineurin inhibitor–free immunosuppression failed to demonstrate cardiovascular risk advantages of the latter. In fact, no real differences in renal function or arterial hypertension were noticed between both regimens, but a worse control of lipids was described with sirolimus-based immunosuppression.

Tacrolimus/MMF shows a favorable cardiovascular risk profile when compared with other immunosuppressive combinations. Whether differences on cardiovascular risk factors will result in a decreased incidence of cardiovascular events in the long term remains to be demonstrated.

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