NDT

Nephrology Dialysis Transplantation

Original Article

Efficacy and safety of tacrolimus compared with ciclosporin A in renal transplantation: three-year observational results

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Abstract

Background. The European tacrolimus versus ciclosporin A microemulsion (CsA-ME) renal transplantation study showed that tacrolimus was significantly more effective in preventing acute rejection and had a superior cardiovascular risk profile at 6 months.

Methods. The endpoints of this investigator-initiated, observational, 36-month follow-up were acute rejection incidence rates, rates of patient and graft survival and renal function. An additional analysis was performed using the combined endpoints BPAR, graft loss and patient death. Data available from the original ITT population (557 patients; 286 tacrolimus and 271 CsA-ME) were analysed.

Results. A total of 231 tacrolimus and 217 CsA-ME patients participated. At 36 months, Kaplan–Meier-estimated BPAR-free survival rates were 78.8% in the tacrolimus group and 60.6% in the CsA-ME group, graft survival rates were 88.0% and 86.9% and patient survival rates were 96.6% and 96.7%, respectively. The estimated combined endpoint-free survival rate was 71.4% with tacrolimus and 55.4% with CsA-ME ($P \leq 0.001$, chi-square test). Significantly more CsA-ME patients crossed over to tacrolimus during the 3-year follow-up: 21.2% versus 2.6%, $P \leq 0.0001$, chi-square test. Most patients in the tacrolimus arm discontinued steroids and received monotherapy and fewer tacrolimus patients remained on a triple regimen. Mean serum creatinine concentration was 145.4 ± 90.9 μmol/L with tacrolimus and 149.0 ± 92.1 μmol/L with CsA-ME. Significantly more CsA-ME patients had a classified cholesterol value >6 mmol/L (26.3% versus 12.6%, $P \leq 0.0003$, chi-square test).

Conclusions. Patients treated with tacrolimus had significantly higher combined endpoint-free survival rates and lower acute rejection rates with less immunosuppressive medication at 36 months.

Keywords: acute rejection; calcineurin inhibitors; follow-up; graft survival; patient survival

Introduction

Immunosuppressive treatment with tacrolimus has proven efficacy in short-term clinical outcomes. The excellent results obtained in preventing rejection in the short term have shifted the focus of clinical research to the evaluation of the long-term efficacy and safety of maintenance treatment with tacrolimus and ciclosporin A microemulsion (CsA-ME).

The results of clinical studies have shown comparable longer-term patient and graft survival with tacrolimus and CsA-ME. For example, a US comparative study [1] showed equivalent patient and graft survival at 3 years with tacrolimus or CsA-ME maintenance immunosuppression and a multivariate analysis of retrospective US Renal Transplant Scientific Registry data [2] demonstrated that both tacrolimus and CsA-ME conferred approximately equal protection against the risk of graft loss secondary to
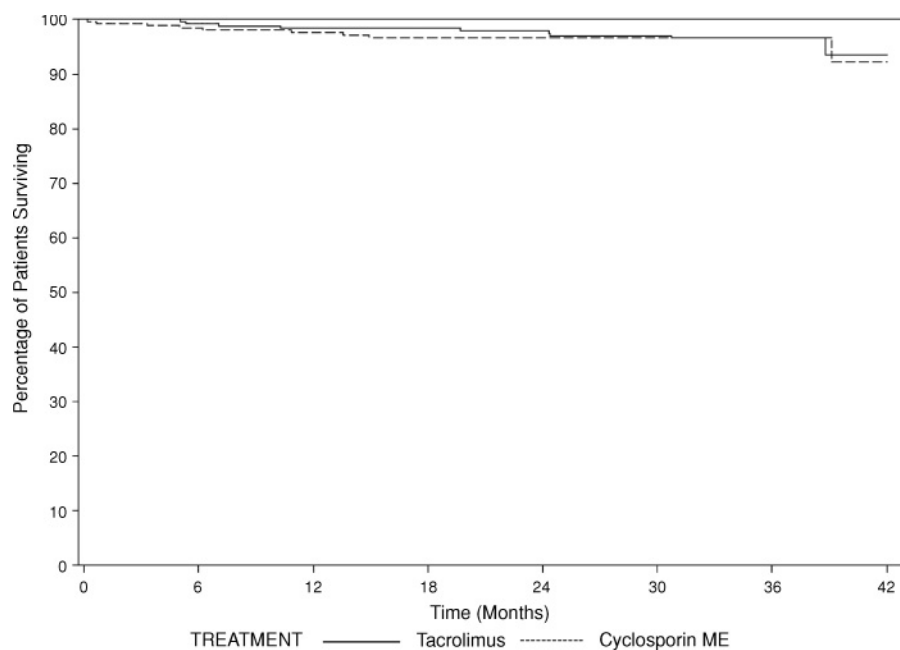
Fig. 1. The estimated patient survival (Kaplan–Meier method) at the 36-month follow-up using the ITT population was 96.6% with tacrolimus and 96.7% with ciclosporin ME (P = ns).

Table 1: Immunosuppressive regimen at 36 months

	Tacrolimus $n = 231$	Ciclosporin-ME $n = 217$
Monotherapy with calcineurin inhibitor	32 (13.9%)[a]	4 (1.8%)
Triple regimen[b]	44 (19.0%)	65 (29.9%)
Treatment crossover		
Ciclosporin-ME	6 (2.6%)	–
Tacrolimus	–	46 (21.2%)[c]

Available data from the ITT population at Month 36.
[a]$P < 0.0001$ (chi-square test). [b]Calcineurin inhibitor + AZA or MMF + steroids. [c]$P < 0.0001$ (chi-square test).

chronic allograft failure at 4 years. However, at 5 years, the projected graft half-life was longer, and chronic rejection was less frequent with tacrolimus-based immunosuppression [3]. And, results of a longer-term European comparative study [4] demonstrated better 6-year graft survival and longer estimated graft half-life with tacrolimus.

In terms of safety, clinical research results indicate advantages with maintenance tacrolimus. In three separate comparative studies, longer-term renal function, as measured by serum creatinine, was lower at 3 years [1] in patients maintained on tacrolimus, and glomerular filtration rate (GFR) was better with tacrolimus at 5 years [5] and at 6 years [4]. Maintenance tacrolimus treatment resulted in a lower renal resistance index and less need for antihypertensive medications compared with CsA-ME [6].

The 6-, 12- and 24-month data from our multicentre, randomized, comparative clinical trial demonstrated that tacrolimus reduced the number and severity of biopsy-proven acute rejection (BPAR) compared to CsA-ME [7–9]. The study results at 24 months showed significantly lower mean serum creatinine levels as well as blood lipid levels in patients maintained on tacrolimus [9]. The aim of this

investigator-initiated, observational follow-up study was to evaluate the clinical outcome at 36 months post-transplant in terms of the rate of acute rejection, graft and patient survival and renal allograft function.

Methods

The study design, patient selection and treatment plan are described in detail in the 6-month study publication [7]. The original study was a randomized, open-label study, initiated in 1997 and conducted in 50 transplant centres in seven European countries in adults with end-stage renal disease. Patients were randomized to receive tacrolimus ($n = 286$) or CsA-ME ($n = 271$) combined with azathioprine and corticosteroids. Target tacrolimus whole blood trough levels were 10–20 ng/mL during the first 3 months and 5–15 ng/mL between Months 4–6. Target CsA-ME whole blood trough levels were 100–400 ng/mL during the first 3 months and 100–200 ng/mL thereafter. In both groups, azathioprine (1–2 mg/kg/day) could be discontinued from Day 92 onwards. Corticosteroid treatment was
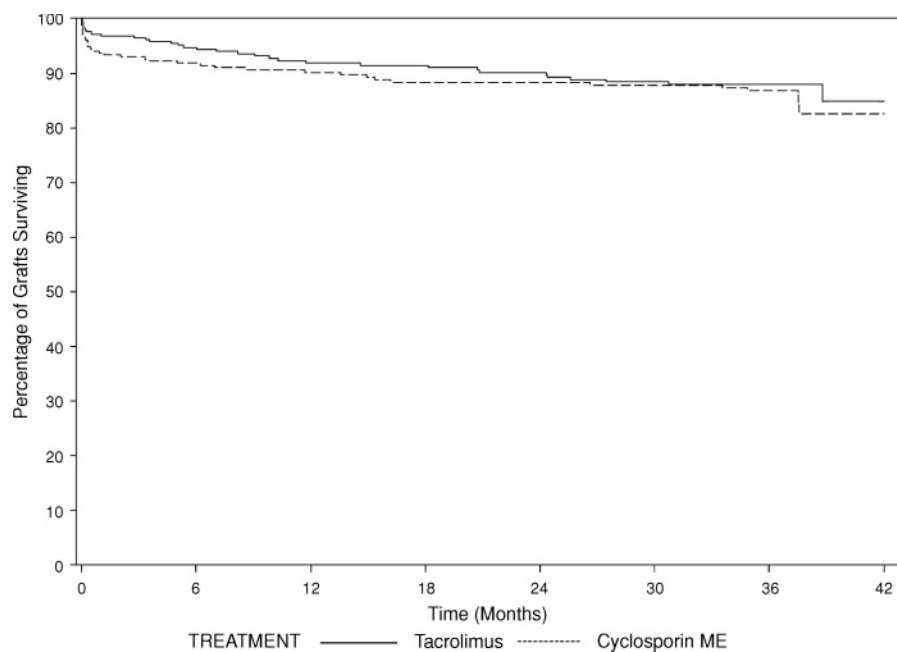
Fig. 2. The estimated graft survival (Kaplan–Meier method) at the 36-month follow-up using the ITT population was 88.0% with tacrolimus and 86.9% with ciclosporin ME (*P* = ns).

Table 2. Classified mean serum creatinine values in ITT and SORT populations

	Tacrolimus		Ciclosporin ME	
	n = 231[a]	*n* = 204 (SORT)[b]	*n* = 217[a]	*n* = 152 (SORT)[b]
≤100 µmol/L	46 (19.9%)	46 (22.6%)	44 (20.3%)	28 (18.4%)
>100–≤150 µmol/L	98 (42.4%)	91 (44.6%)	91 (41.9%)	77 (50.7%)
>150–≤250 µmol/L	52 (22.5%)	48 (23.5%)	47 (21.7%)	33 (21.7%)
>200–≤250 µmol/L	12 (5.2%)	11 (5.4%)	11 (5.1%)	9 (5.9%)
>250 µmol/L	9 (3.9%)	6 (2.9%)	11 (5.1%)	4 (2.6%)

[a]Available data from the ITT population at Month 36: values were missing from 14 (6.1%) tacrolimus and from 13 (6%) ciclosporin ME patients.
[b]Patients who Stayed On Randomized Treatment (SORT) at Month 36.

rapidly tapered to 5 mg from Day 43 onwards. After completion of the main study, target levels of calcineurin inhibitors were specified following centre practice.

Since the completion of the main study in 1999, we have continued to observe patients at regular intervals in an investigator-initiated follow-up study. Variables assessed during the follow-up were patient and graft survival rates, acute rejection assessed by clinical signs and symptoms, BPAR, chronic allograft nephropathy [10] and assessment of graft function as determined by serum creatinine (Cockroft–Gault formula [11]). The incidence and number of adverse events and laboratory parameters were also recorded throughout the 36-month follow-up period.

The intent-to-treat (ITT) population was used for all analyses of efficacy and safety. Some safety data were analysed in addition using the SORT subsample (Stayed On Randomized Treatment). As this was an observational study, no statistical tests were planned to make comparisons between treatment groups. The time to onset of BPAR was analysed with Kaplan–Meier survival procedures. Patient- and graft-survival estimates were analysed by Kaplan–Meier meth-

ods and the Wilcoxon test was used to compare groups. A *P*-value of <0.05 was considered to be statistically significant.

For purposes of this follow-up study, data were also analysed using a composite endpoint consisting of BPAR, graft loss and patient death. A composite endpoint includes as many clinically relevant endpoints as possible in the efficacy assessment of a treatment without necessitating an increase in the sample size to an unacceptable level [12].

Results

Demographic and baseline characteristics of patients providing data at the 36-month follow-up were similar between the treatment groups and the original demographic data [7]. This was an almost exclusively Caucasian population and the mean age in both arms was 43 years at transplantation. Of the 557 ITT patients in the original study, 231 (80.8% of 286) patients in the tacrolimus group and 217 (80.1% of 271) patients in the CsA-ME group
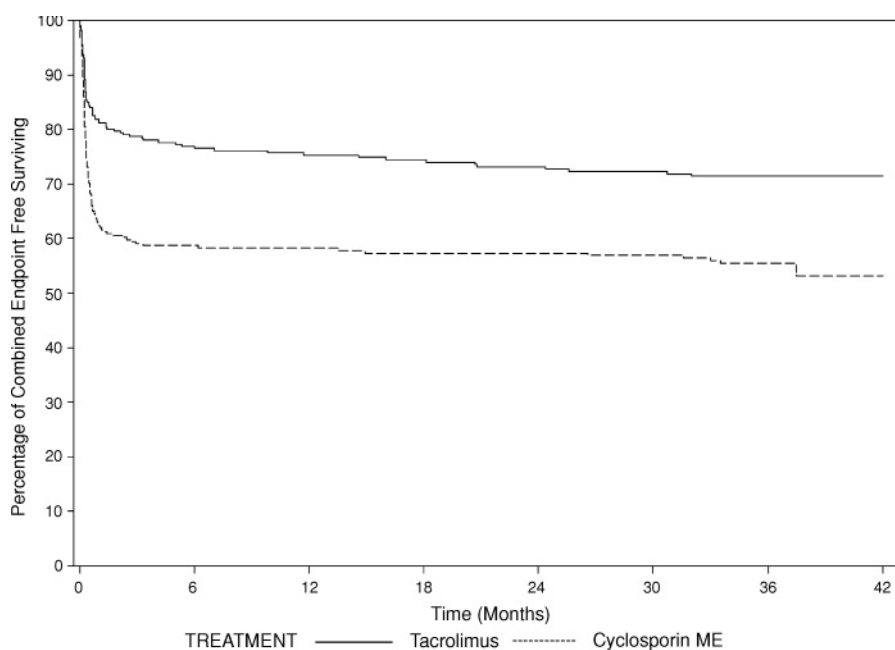
Fig. 3. The estimated combined endpoint-free survival rate (Kaplan–Meier method) at the 36-month follow-up using the ITT population was 71.4% with tacrolimus and 55.4% with ciclosporin ME ($P \leq 0.001$).

Table 3. Concomitant medications taken at 36 months

	Tacrolimus $n = 231$	Ciclosporin-ME $n = 217$
Antihypertensive	170 (73.6%)	176 (81.1%)[a]
Insulin	23 (10%)	19 (8.8%)
Oral antihyperglycaemic	6 (2.6%)	4 (1.8%)
Antihyperlipidaemic	45 (19.5%)	73 (33.6%)[b]

Available data from the ITT population at Month 36.
[a]$P = 0.058$ (chi-square test). [b]$P = 0.001$ (chi-square test).

provided data at 36 months from 43 of the original 50 centres that had participated in the main 6-month trial. Of these patients, the SORT subsample consisted of 204 patients in the tacrolimus and 152 patients in the CsA-ME group.

Patient and graft survival at Month 36 were equivalent between the treatment groups (Figures 1 and 2). The estimated patient survival at Month 36 was 96.6% for the tacrolimus group and 96.7% for the CsA-ME group. The corresponding estimated graft survival was 88.0% and 86.9%, respectively. Four patients in the tacrolimus and one patient in the CsA-ME group died after Month 24. In the tacrolimus group, three grafts were lost after Month 24: two from unknown or other causes and one due to chronic rejection. In the CsA-ME group, six grafts were lost: one from unknown causes, four as a result of chronic rejection and one due to recurrence of primary disease.

The rates of first clinical acute rejection (diagnosed using signs and symptoms) from 0 to 36 months were 81 (35.1%) patients treated with tacrolimus and 114 (52.5%) patients treated with CsA-ME. The Kaplan–Meier estimated rate of the BPAR-free survival from study initiation until follow-up assessment was 78.8% in the tacrolimus and 60.6% in the CsA-ME group. During Months 24–36 a new episode of BPAR was reported in three patients in the tacrolimus group and in two patients in the CsA-ME-treated group. Histological grade of acute rejection, according to the Banff 93 classification [10], was mild with two borderline, two grade I and one grade II reported cases. A new onset of chronic allograft nephropathy (Banff category 5) during the 24- to 36-month time frame of this analysis was reported in one (0.4%) tacrolimus-treated and in three (1.4%) CsA-ME-treated patients.

The estimated combined endpoint-free survival rate (using the components BPAR, graft loss and patient death) was significantly higher in the tacrolimus group than in the CsA-ME group: 71.4% versus 55.4%, $P \leq 0.001$, chi-square test (Figure 3). The analysis of the composite endpoint in the SORT subsample also revealed a significant difference between treatment groups at 36 months: tacrolimus, 80.8% versus CsA-ME, 72.3%, $P = 0.05$.

More tacrolimus than CsA-ME patients were able to be maintained on a calcineurin inhibitor alone at Month 36 and the incidence of crossover from CsA-ME to tacrolimus was significantly greater than the incidence of crossover from tacrolimus to CsA-ME (21.2% versus 2.6%; $P < 0.0001$, chi-square test) (Table 1). Fewer tacrolimus (66.7%) than CsA-ME (77.9%) patients were receiving steroids at Month 36 ($P < 0.01$, chi-square test); the mean administered daily steroid dose was similar between groups (tacrolimus 4.8 mg, CsA-ME 5.3 mg; only calculated for patients being on steroids at Month 36).

At Month 36, the mean daily dose of tacrolimus was 0.08 mg/kg compared with 2.84 mg/kg in the CsA-ME group. Correspondingly, mean whole blood trough levels of tacrolimus were 8.32 ng/mL and mean trough levels of CsA-ME were 137.3 ng/mL.

Renal function at 36 months, as measured by mean serum creatinine, was similar in both groups: 145.4 µmol/L (SD ± 90.9) in the tacrolimus group and 149 µmol/L (SD ± 92.1) in the CsA-ME group. An analysis of classified serum creatinine concentrations of patients in the ITT and SORT showed that ∼60% of the patients in both the tacrolimus and CsA-ME groups (ITT and SORT samples) had a classified creatinine value of ≤150 µmol/L and ∼30% of all patients had >150 µmol/L (Table 2). Estimated mean creatinine clearance values (Cockroft–Gault formula) were similar between groups: 67.3 mL/min (SD ± 23.6) with tacrolimus and 64.0 mL/min (SD ± 23.9) with CsA-ME. Similar results were found in the two SORT subsample groups.

Mean serum cholesterol levels at 36 months in the tacrolimus versus the CsA-ME group were 5.2 mmol/L (SD ± 1.1) versus 5.4 mmol/L (SD ± 1.1). Mean triglyceride levels were also comparable between groups at 1.7 mmol/L (SD ± 1.0) in the tacrolimus versus 1.8 mmol/L (SD ± 1.0) in the CsA-ME group. In the SORT subsamples a trend for lower mean cholesterol levels in the tacrolimus group versus the CsA-ME group [5.1 mmol/L (SD ± 1.2) and 5.5 mmol/L (SD ± 1.1), respectively] was observed, and mean triglyceride levels were comparable between groups [1.7 mmol/L (SD ± 1.0) and 1.8 mmol/L (SD ± 1.0), respectively]. A comparison of classified serum cholesterol values (serum cholesterol values > 6.0 mmol/L classified as hypercholesteraemic) using the ITT and SORT samples showed that significantly more patients in the CsA-ME group than in the tacrolimus ITT or SORT group were hypercholesteraemic ($P < 0.0003$, chi-square test). Specifically, in the ITT population there were 29 (12.6%) tacrolimus-treated patients who were hypercholesteraemic compared with 57 (26.3%) CsA-ME patients.

The use of antihypertensive medications was equivalent in both treatment groups. Similarly, the number of patients who were taking two or more antihypertensive medications was comparable: 99 (42.9%) tacrolimus and 107 (49.3%) CsA-ME patients. The reported further concomitant medication, including insulin and oral antihyperglycaemics, was similar between groups with the exception of the use of medications for hyperlipidaemia which was higher in the CsA-ME group (Table 3).

The incidence of adverse events, including malignancies, was comparable between groups. An exception here was treatment-related cosmetic adverse events that were reported more often in the CsA-ME group (Table 4). Within the ITT population, twice as many bone fractures were reported in CsA-ME patients than in patients in the tacrolimus group: the incidence, however, was similar in SORT patients. For three (1.3%) patients in the tacrolimus group and three (1.4%) in the ciclosporin group who did not use insulin in the main study, insulin use was reported at least once during the follow-up period.

Discussion

In this follow-up of the first major multicentre clinical trial in kidney transplantation to compare the efficacy and safety of a tacrolimus-based regimen with the microemulsion for-

mulation of ciclosporin we found similar efficacy outcomes in the two treatment groups during the 25- to 36-month study period. Further, rates of patient death and graft loss at 36 months were similar between groups. We found advantages with respect to longer-term tacrolimus treatment over ciclosporin-ME in terms of less hypercholesterolaemia and significantly less crossover of maintenance immunosuppressant.

When analysing the combined endpoint composed of BPAR, graft loss and patient death, the estimated endpoint-free survival rate was significantly higher in the tacrolimus treatment group at 36 months post-transplantation. This result is most likely attributable to the reduction of BPAR, a component of the combined endpoint, and most likely the first of the three events to occur during the 6 months post-transplantation as demonstrated in our original study [7]. This means on the other hand that beyond the first 6 months after transplantation, this combined efficacy and safety endpoint occurs at a similar rate in both treatment groups. Nevertheless, although the incidence of each event used in the combined endpoint analysis was similar in the follow-up phase of this study, the efficacy of tacrolimus during the first 6 months seemed to influence the outcome, in terms of the combined endpoint, longer term.

Of interest, we found a significant difference in the number of patients randomized to ciclosporin-ME who were crossed-over to tacrolimus. We feel that our findings related to crossover have clinical relevance as they depict a 'real-life' treatment scenario in longer term renal transplant care. Similar to our results, Vincenti *et al.* [5] also found a significantly greater crossover from ciclosporin to tacrolimus at 5 years post-renal transplant. The decision for crossover may, besides responding to specific adverse effects like acute rejection [7], post-transplant diabetes mellitus or hirsutism, also be driven by subjective impressions of the treating physician or the patient of benefits of a specific treatment, thereby introducing bias.

More patients in the tacrolimus group in our study discontinued steroids and received monotherapy as compared with the ciclosporin-ME group. Longer-term benefits of reducing steroids may be a reduction in cardiovascular risk [13], a minimization of adverse events due to immunosuppressive load and enhancement of patient compliance as a result of decreasing the number of necessary medications.

In the present study, renal function was comparable in the two treatment groups. Results of a 5-year US multicentre comparative study showed significantly higher serum creatinine in patients maintained on ciclosporin compared with tacrolimus [5]. Other studies have shown an improvement in serum creatinine when ciclosporin-ME is either withdrawn or replaced [14,15]. In a recent systematic Cochrane review, that analysed 4102 renal transplant recipients [16], it has been reported that graft survival as well as renal function is superior with tacrolimus-based immunosuppression compared to cyclosporin-based immunosuppression, thereby confirming and extending the results of several prospective randomized trials [1,3–5,9].

Based on these reports, we had anticipated that renal function would be most favourable in the tacrolimus SORT subsample; however, this assumption was not supported by

Table 4. Adverse events Months 24–36

	Tacrolimus		Ciclosporin ME	
	$n = 231$ (ITT)[a]	$n = 204$ (SORT)[b]	$n = 217$ (ITT)[a]	$n = 152$ (SORT)[b]
Malignancies	7 (3%)	4 (2%)	5 (2.3%)	3 (2%)
Cosmetic	8 (3.5%)[e]	7 (3.4%)	28 (12.9%)	22 (14.5%)
Severe infections[c]	9 (3.9%)	8 (3.9%)	10 (4.6%)	6 (4%)
Bone fractures	7 (3%)[f]	7 (3.4%)	16 (7.4%)	6 (4%)
Major CV event[d]	10 (4.3%)	10 (4.9%)	9 (4.2%)	6 (4%)
Important other	16 (6.9%)[g]	15 (7.4%)	27 (12.4%)	15 (9.9%)

[a]Available data from ITT population at Month 36. [b]Patients who Stayed On Randomized Treatment (SORT) at Month 36. [c]Infections requiring hospitalization. [d]Includes myocardial infarction, heart failure, percutanous transluminal coronary angioplasty, atrial fibrillation. [e]$P < 0.001$ (chi-square test). [f]$P = 0.002$ (chi-square test). [g]$P = 0.048$ (chi-square test).

study results. Results did reveal that roughly one-third of all patients in both the ITT and SORT samples in both treatment groups had mean serum creatinine concentration parameters that exceeded 150 µmol/L, an unfavourable prognostic indicator for renal function longer term. Though we cannot explain this finding definitively, we speculate that average tacrolimus whole blood trough levels ranging ~10.1 ng/mL, 8.7 ng/mL and 8.3 ng/mL at 1, 2 and 3 years post-transplant, which would be considered clearly as high by most centres today, could have contributed via its nephrotoxic potential to this comparable renal function at 3 years.

We found more hypercholesterolaemia in the ciclosporin-ME treatment group despite a greater use of antihyperlipidaemic medications in that group. A similar comparative study [4] found significant differences between tacrolimus and ciclosporin-ME in regard to cardiovascular risk factors at 3 years. At 5-year follow-up, a US comparative study showed a significantly greater use of antihypertensive medications and serum lipid lowering medications with ciclosporin compared with tacrolimus [5]. There may be a link between hypercholesterolaemia and an increased risk of late graft loss in patients with at least one episode of acute rejection as suggested by the results of one study [17]. Interestingly, in this European trial in renal transplant recipients at 3 years post-transplant both the insulin use and the use of oral antihyperglycaemics were not different between tacrolimus and ciclosporin-ME treatment groups. With regard to the known diabetogenic risk associated with tacrolimus use, the absence of a difference in treated diabetes might be due to the high rate of tacrolimus patients off steroids, the low dose of steroids in the patients remaining on steroids, the rather low tacrolimus levels at 3 years and the known lower risk for post-transplant diabetes mellitus in a European population [18]. Unfortunately at the time when the present 3-year follow-up was planned, defining and assessing post-transplant diabetes mellitus as suggested by the 2003 International Consensus Guidelines [18] (diagnostic guidelines according to ADA and WHO) was not standard in transplantation trials. Therefore, post-transplant diabetes mellitus according to ADA/WHO guidelines has not been assessed in the present follow-up.

A potential limitation of the present analysis is that the follow-up study sample was limited to ~80% of the original cohort; 7 of the original 50 centres did not participate in our investigator-initiated follow-up. However, the percentage of the original sample that was available for our follow-up analysis is in line with that used in the analysis of other long-term studies [1,5]. Furthermore, our findings in both treatment arms may nevertheless be considered representative for the whole trial, since the 43 contributing centres provided complete follow-up data. Therefore, the data obtained by our observational follow-up appear to be valid and do not, in our view, introduce undue bias.

In conclusion, the efficacy of tacrolimus was better at 36 months, as demonstrated by the significantly higher estimated combined endpoint-free survival rate (BPAR, graft loss and patient death) in this treatment group. From a clinical and patient prospective, maintenance treatment with tacrolimus demonstrated advantages in that more patients were able to be maintained on randomized treatment or tacrolimus monotherapy, fewer concomitant immunosuppressive medications were needed in this group and patients treated with tacrolimus had less hypercholesterolaemia with less antihyperlipidaemic use as found in this follow-up comparative study.

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