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ORIGINAL ARTICLE

Efficacy and safety of tacrolimus compared with ciclosporin-A in renal transplantation: 7-year observational results

Bernhard K. Krämer,[1,*] Giuseppe Montagnino,[2,*] Bernd Krüger,[1,*] Raimund Margreiter,[3] Christoph J. Olbricht,[4] Roberto Marcen,[5] Urban Sester,[6] Ulrich Kunzendorf,[7] Karl-Heinz Dietl,[8] Paolo Rigotti,[9] Claudio Ronco,[10] Silke Hörsch,[11] Bernhard Banas,[12,†] Ferdinand Mühlbacher[13,†] and Manuel Arias[14,†] for the European Tacrolimus versus Ciclosporin Microemulsion Renal Transplantation Study Group[‡]

1 Universitätsmedizin Mannheim, Vth Department of Medicine, Medical Faculty of the University of Heidelberg, Mannheim, Germany
2 Division of Nephrology and Dialysis, Ospedale Maggiore di Milano IRCCS, Milano, Italy
3 Landeskrankenhaus, University of Innsbruck, Innsbruck, Austria
4 Katharinenhospital, Stuttgart, Germany
5 Hospital Ramón y Cajal, Madrid, Spain
6 Universitätsklinik des Saarlandes, Homburg, Germany
7 Klinik für Nephrologie, University of Kiel, Kiel, Germany
8 Universitätsklinik Münster, Münster, Germany
9 Universitá di Padova, Padua, Italy
10 Universitá di Vicenza, Vicenza, Italy
11 Koehler eClinical GmbH, Freiburg, Germany
12 Abteilung für Nephrologie, University of Regensburg, Regensburg, Germany
13 Allgemeines Krankenhaus Wien, Medical University of Vienna, Austria
14 Hospital Marqués de Valdecilla, Santander, Spain

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Correspondence
Prof. Dr. Bernhard Krämer, Universitätsmedizin Mannheim, Vth Department of Medicine, Medical Faculty Mannheim of the University of Heidelberg, Theodor-Kutzer-Ufer 1-3, Mannheim 68167, Germany.
Tel.: +49 621 3833660;
fax: +49 621 3833804;
e-mail: bernhard.kraemer@umm.de

*Contributed equally as first author.

†Contributed equally as senior author.

‡Other Investigators are listed in the Supporting Information.

Conflict of interest
The main trial and the investigator-initiated follow-up were sponsored by Astellas. BKK participated in clinical trials sponsored by Astellas, BMS, Novartis, Roche, and Wyeth, received lecture fees from Astellas, Novartis,

Summary

The European Tacrolimus versus Ciclosporin-A Microemulsion (CsA-ME) Renal Transplantation Study demonstrated that tacrolimus decreased acute rejection rates at 6 months. Primary endpoints of this investigator-initiated, observational 7-year follow-up study were acute rejection rates, patient and graft survival rates, and a composite endpoint (BPAR, graft loss, and patient death). We analyzed data from the original intent-to-treat population (n = 557; 286 tacrolimus, 271 CsA-ME). A total of 237 tacrolimus and 208 CsA-ME patients provided data. At 7 years, Kaplan–Meier estimated rates of patients free from BPAR were 77.1% in the tacrolimus arm and 59.9% in the CsA-ME arm, graft survival rates amounted to 82.6% and 80.6%, and patient survival rates to 89.9% and 88.1%. Estimated combined endpoint-free survival rates were 60.2% in the tacrolimus arm and 47.0% in the CsA-ME arm (P = <0.0001). A higher number of patients from the CsA-ME arm crossed over to tacrolimus during 7 year follow-up: 19.7% vs. 7.9% (P = <0.002). More patients in the tacrolimus group stopped steroids and received immunosuppressive monotherapy. Significantly, more CsA-ME patients received lipid-lowering medication and experienced cosmetic and cardiovascular adverse events. Tacrolimus-treated renal transplant recipients had significantly higher combined endpoint-free survival rates mainly driven by lower acute rejection rates despite less immunosuppressive medication at 7 years.

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This investigator-initiated follow-up study has been registered with the Cochrane Renal Group (http://www.cochrane-renal.org/dbsearch.php) with the study ID number CRG040700114.

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Introduction

Immunosuppression with tacrolimus in renal transplant recipients is highly efficacious regarding short-term clinical outcomes. In recent years, superior results achieved in preventing acute rejection in the short term have changed the aims of clinical transplant research to the evaluation of medium- and longer term efficacy and safety of maintenance immunosuppression after renal transplantation.

Comparative studies have found similar longer term patient and graft survival with tacrolimus and ciclosporin-A microemulsion (CsA-ME). A study in North America [1] demonstrated similar patient and graft survival after 3 years with tacrolimus versus CsA-ME immunosuppression. Also, a retrospective analysis of US Scientific Registry of Transplant Recipients (SRTR) data [2] showed that both tacrolimus and CsA-ME were associated with similar protection against the risk of graft loss due to chronic renal allograft damage at 4 years. Similarly, a retrospective study using the USRDS database during the years 1996–2000 found similar graft survival with tacrolimus compared with cyclosporine [3]. In contrast, graft half-life was longer, with less chronic rejection in the tacrolimus arm after 5 years in an European study [4]. Furthermore, a long-term European trial [5] found higher 6 year graft survival and higher estimated graft half-life in the tacrolimus arm. Furthermore, results of the large (n = 1645) ELITE Symphony study demonstrated superior renal function (e.g., estimated glomerular filtration rate = eGFR), better graft survival rates and less biopsy-proven acute rejection rates (BPARs) with low-dose tacrolimus when compared with both low-dose and standard-dose cyclosporine at 1 year post-transplant [6]. In a follow-up study after 3 years in 958 renal transplant recipients eGFR was higher, graft survival was highest and acute rejection rates were lowest with low-dose tacrolimus compared with cyclosporine, although differences tended to diminish possibly due to major treatment crossover between groups and smaller sample size [7].

Regarding safety, some clinical trials found advantages with tacrolimus. Long-term kidney function, when measured as serum creatinine concentrations, was lower after 3 years in patients treated with tacrolimus, and when reported as GFR was superior with tacrolimus at 3 years, at 5 years and at 6 years in four different comparative trials [1,5,7,8]. The renal resistance index was lower and the number of antihypertensives were lower with tacrolimus compared with CsA-ME [9].

The 6-, 12-, 24-, and 36-month results from our multicenter, randomized, and comparative trial found tacrolimus to reduce the rate and severity of BPARs

in comparison with CsA-ME [10–13]. At 2 years post-transplant, we have reported significantly lower mean serum creatinine concentrations as well as lipid levels in patients in the tacrolimus arm [12]. The main aim of our follow-up was to study clinical outcomes at 7 years post-transplant, that is BPAR rates, graft and patient survival rates, and transplant kidney function.

Subjects and methods

Trial design, patient selection, and treatment protocol have been reported in some detail in the 6-month study publication and subsequent follow-up reports [10–13]. The main trial was a randomized, open-label study, performed in 50 European transplant centers in patients with end-stage renal disease (CKD stage 5D). Adult renal transplant recipients were randomized to and received tacrolimus (n = 286) or CsA-ME (n = 271) in combination with azathioprine and corticosteroids, but without the use of induction therapy (e.g., ATG, OKT3). Tacrolimus whole blood trough target levels were set at 10–20 ng/ml during the first 3 months and at 5–15 ng/ml between months 4 and 6. CsA-ME whole blood trough target levels were set at 100–400 ng/ml during the first 3 months and at 100–200 ng/ml between months 4–6. Azathioprine (recommended dosing range 1–2 mg/kg/day) could be stopped after day 92. Steroids were rapidly tapered to 5 mg daily after 6 weeks. After the main study, calcineurin inhibitor target levels were set according to center practice.

After completion of the main study in 1999, renal transplant recipients have been followed in an investigator-initiated follow-up study. Outcomes determined during follow-up were patient and graft survival rates, clinically diagnosed acute rejection, as well as BPAR [14], and renal transplant function based on serum creatinine concentrations (eGFR using the Cockroft Gault formula [15]). Adverse events and additional laboratory parameters were also assessed during the 7 year follow-up interval. Additionally, in this follow-up study, we also analyzed the obtained data by use of a composite endpoint consisting of BPAR, renal allograft loss, and patient death. A composite endpoint consists of as many clinically relevant endpoints as possible for the efficacy assessment of a treatment to avoid the need for an unacceptably high increase in sample size [16]. When the present investigator-initiated, observational follow-up was registered with the Cochrane Renal Group Trials Registry primary outcomes were defined as BPAR, graft survival, patient survival, and a composite endpoint of BPAR, graft loss, and patient death. Secondary outcomes were defined as hypercholesterolemia, hypertension, diabetes mellitus, cardiovascular morbidity, cardiovascular mortality, and (additional) side effects.

The original intent-to-treat (ITT) population which included all randomized patients, who were transplanted and received at least one dose of study medication (n = 286 in the tacrolimus arm; n = 271 in the CsA-ME) was used for all analyses of efficacy. As this was an observational study, all statistical analyses are of a descriptive nature. Patient and graft survival and the rate of patients free of BPAR were estimated by Kaplan–Meier methods and Gehan's generalized Wilcoxon test was used to compare the time to onset of events between treatment groups. Frequencies of immunosuppressive regimen, concomitant medication, and adverse events are based on the number of patients who provided follow-up data. Chi-squared tests were used to compare frequencies of for example side effects between treatment groups. Student's t-tests were used to compare creatinine (log-transformed) and creatinine clearance values at year 7. All P-values are considered exploratory.

Results

Baseline patient characteristics of renal transplant recipients contributing data for the 7-year follow-up were similar between treatment groups and to the main study (and follow-up) patient characteristics [10–13]. This was a mostly Caucasian, low-immunologic risk population (first renal transplant in 93%, 2.5 HLA mismatches, PRA levels <50%) of renal (postmortal donor in 96%) transplant recipients with a mean age in both groups of 43 years at transplantation. Of the 557 ITT patients in the main study, 237 (82.9% of 286) patients in the tacrolimus arm and 208 (76.8% of 271) patients in the CsA-ME arm contributed data at 7 years with 43 of the original 50 centers from the main 6-month trial providing data.

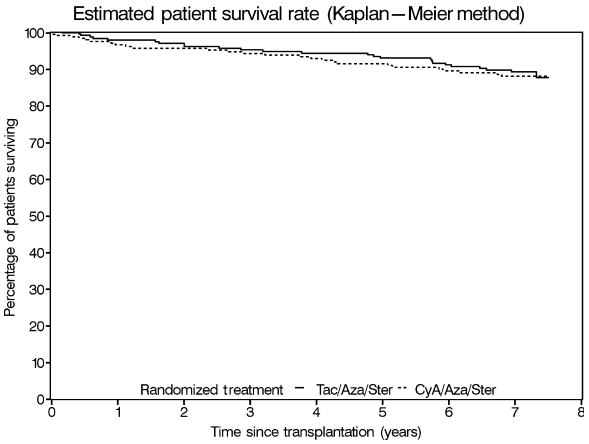

Figure 1 The estimated patient survival (Kaplan–Meier method) at 7 years follow-up using the ITT population was 89.9% with tacrolimus and 88.1% with ciclosporin-ME (P = ns).

Patient and graft survival rates at year 7 were similar between treatment arms (Figs 1 and 2). The estimated patient survival rate at year 7 was 89.9% in the tacrolimus arm and 88.1% in the CsA-ME arm. Estimated graft survival rates were 82.6% and 80.6% in the tacrolimus abd CsA-ME arms. Twenty-five patients in the tacrolimus arm and 26 patients in the CsA-ME arm died during the observation period. In the tacrolimus arm, 46 grafts were lost during the observation period, and in the CsA-ME arm, 48 grafts were lost.

Kaplan–Meier estimated rates of BPAR-free survival from start of trial until final follow-up investigation at year 7 were 77.1% in the tacrolimus and 59.9% in the CsA-ME arm. During months 36–84, new BPAR episodes were reported in two renal transplant recipients in the tacrolimus arm and in none in the CsA-ME arm. Estimated combined endpoint-free survival rates (consisting of BPAR, renal allograft loss, and patient death) were significantly higher in the tacrolimus arm than in the CsA-ME arm with 60.2% vs. 47.0% ($P < 0.001$, Wilcoxon test) (Fig. 3).

Overall, 189 (80.0%) tacrolimus and 157 (75.5%) CsA-ME patients provided information regarding immunosuppressive regimen at year 7. More tacrolimus than CsA-ME patients were on a calcineurin inhibitor monotherapy at year 7, less tacrolimus than CsA-ME patients received triple immunosuppression. Furthermore, incidence of crossover from CsA-ME to tacrolimus was significantly higher than incidence of crossover from tacrolimus to CsA-ME (19.7% vs. 7.9%; $P = 0.002$, chi-squared test) (Table 1). Mean daily calcineurin inhibitor doses were 0.06 mg/kg (SD ± 0.04) for tacrolimus and 2.51 mg/kg (SD ± 1.31) for cyclosporine at year 7. Mean whole blood tacrolimus trough levels were 7.0 ng/ml (SD ± 2.1) and mean cyclosporine trough levels were 115.6 ng/ml (SD ± 40.9) (after excluding implausibly high trough levels >300 ng/ml; median trough level with all measurements 108.5 ng/ml, after excluding implausibly high values 103.0 ng/ml).

Fewer tacrolimus (60.3%) than CsA-ME (75.8%) patients received corticosteroids at year 7 ($P < 0.005$, chi-squared test); mean administered daily corticosteroid doses were similar between treatment arms (tacrolimus 5.1 mg (SD ± 2.1), CsA-ME 5.8 mg (SD ± 3.9); calculated only for renal transplant recipients being on steroids at year 7). Slightly fewer tacrolimus (overall 46.0%; MMF 24.9%, azathioprine 21.2%) than CsA-ME (overall 55.4%; MMF 28.7%, azathioprine 26.8) patients were receiving proliferation inhibitors at year 7 ($P < 0.1$, chi-squared test), however, mean administered daily MMF or azathioprine doses were similar between groups [tacrolimus 1180 mg (SD ± 500) and 61 mg (SD ± 19.6), CsA-ME 1123 mg

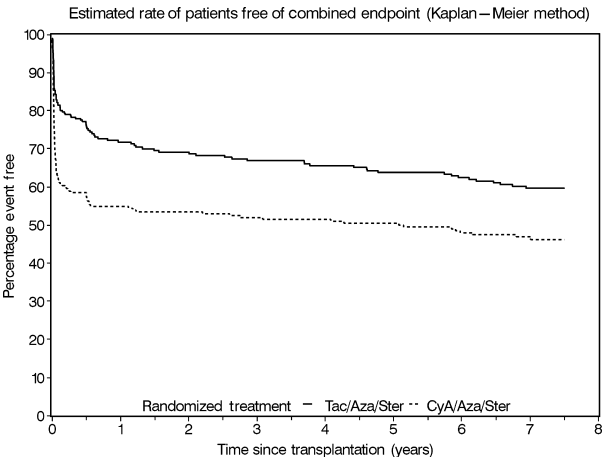

Figure 3 The estimated combined endpoint-free survival rate (Kaplan–Meier method) at 7 years follow-up using the ITT population was 60.2% with tacrolimus and 47.0% with ciclosporin-ME ($P < 0.001$, Wilcoxon test).

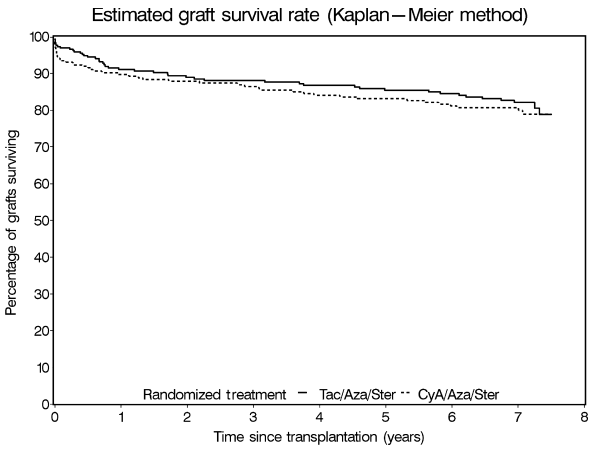

Figure 2 The estimated graft survival (Kaplan–Meier method) at 7 years follow-up using the ITT population was 82.6% with tacrolimus and 80.6% with ciclosporin-ME (P = ns).

Table 1. Immunosuppressive regimen at year 7.

	Tacrolimus, N = 189 (%)	Ciclosporin-ME, N = 157 (%)
Monotherapy with randomized CNI	34 (18.0)*	6 (3.8)
Triple regimen†	46 (24.3)	57 (36.3)
Treatment crossover		
Ciclosporin-ME	15 (7.9)	–
Tacrolimus	–	31 (19.7)‡

Based on available immunosuppressive information at year 7, CNI = calcineurin inhibitor.
*$P < 0.0001$ (chi-squared test).
†Calcineurin inhibitor + AZA or MMF + steroids, $P < 0.02$ (chi-squared test).
‡$P = 0.002$ (chi-squared test).

(SD ± 488) and 66 mg (SD ± 26.8)]. The use of the mTOR inhibitor sirolimus was 5.8% and 6.4% in the tacrolimus and CsA-ME group at year 7.

Renal function at year 7, assessed as mean serum creatinine concentration, was nearly similar in both arms with 139 μmol/l (SD ± 56) in the tacrolimus arm (n = 182) and 147 μmol/l (SD ± 71) in the CsA-ME arm (n = 150) (P = n.s.). eGFR levels (Cockroft–Gault formula) at year 7 were numerically slightly different (P = 0.0396; Student's t-test) between arms with 63.5 ml/min (SD ± 20.8) with tacrolimus (n = 163) and 58.4 ml/min (SD ± 22.1) with CsA-ME (n = 134).

Mean serum cholesterol levels at year 7 in the tacrolimus versus the CsA-ME arm were 5.19 mmol/l (SD ± 1.22) vs. 5.17 mmol/l (SD ± 0.92). Mean plasma glucose levels at year 7 in the tacrolimus versus the CsA-ME arm were 5.92 mmol/l (SD ± 1.76) vs. 5.84 mmol/l (SD ± 1.94).

Use of antihypertensives was comparable in both treatment arms (65.0% vs. 67.3%; diuretics used with other indication than for treatment of hypertension 13.1% vs. 18.8%; tacrolimus versus CsA-ME). Use of additional concomitant medications, that is, insulin and oral antihyperglycemics, was similar between arms, except the use of antihyperlipidemics being higher in the CsA-ME arm (40.4% vs. 28.7%) (Table 2).

Incidences of adverse events were comparable between arms with the exception of cosmetic adverse events like hirsutism, which were reported more frequently in the CsA-ME arm (Table 3). Furthermore, more bone fractures and major cardiovascular events were reported in CsA-ME patients than in patients in the tacrolimus arm (Table 3).

Discussion

In this long-term follow-up of the first large, multicenter, randomized, controlled clinical study in renal transplantation that compared efficacy and safety of a tacrolimus-based immunosuppressive regimen with a ciclosporin microemulsion formulation-based regimen, we found superior efficacy in the tacrolimus treatment group during the 7-year study period. Specifically, when we analyzed the combined endpoint consisting of BPAR, renal allograft loss, and patient death, the estimated combined endpoint-free survival rate was significantly higher in the tacrolimus treatment arm at year 7 post-transplant. This difference is mostly due to reduction of BPAR, the part of the combined endpoint, that with high probability was the event to occur first during the 6 months post-transplant as demonstrated in our main trial [10]. However, after the first 6 months post-transplant, this combined endpoint occured at comparable rates in both treatment arms. As the incidence of each individual event used for the combined endpoint was comparable in the long-term follow-up, the efficacy of tacrolimus during the first 6 months was maintained long-term, that is a lower rate of occurrence of the combined endpoint was found during 7 years of follow-up.

Interestingly there was a significant difference in the number of renal transplant recipients initially randomized to CsA-ME that crossed over to tacrolimus, when compared to the (lower) number of renal transplant recipients initially randomized to tacrolimus that crossed over to CsA-ME. We assume that our results with regard to crossover are of clinical interest as they reflect a so-called 'real life' scenario in long-term care of renal transplant patients. Similarly, Vincenti *et al.* [8] reported a higher crossover rate from ciclosporin to tacrolimus 5 years after renal transplantation. A decision for crossover may either be triggered by adverse events like acute rejection [10], post-transplant diabetes mellitus or cosmetic side effects like hirsutism, or by subjective judgements of the treating physician or the renal transplant recipient of advantages of a specific treatment, and thus may introduce bias.

More renal transplant recipients in the tacrolimus arm of our follow-up stopped steroids, received CNI monotherapy, and less remained on a triple immunosuppressive regimen in comparison with the ciclosporin-ME arm. Long-term advantages of corticosteroid reduction may comprise a decrease in cardiovascular risk, that is less hypertension,

Table 2. Concomitant medications taken at year 7.

	Tacrolimus, N = 237 (%)	Ciclosporin-ME, N = 208 (%)
Antihypertensive	154 (65.0)	140 (67.3)
Insulin	16 (6.8)	17 (8.2)
Oral antihyperglycemic	16 (6.8)	9 (4.3)
Antihyperlipidemic	68 (28.7)	84 (40.4)*

Available data from ITT population at year 7.
*P < 0.01 (chi-squared test).

Table 3. Adverse events until year 7.

	Tacrolimus, N = 237 (%)	Ciclosporin-ME, N = 208 (%)
Malignancies	25 (10.5)	17 (8.2)
Cosmetic*	5 (2.1)	30 (14.4)
Severe infections†	30 (12.7)	28 (13.5)
Bone fractures‡	10 (4.2)	21 (10.1)
Major CV event‡,§	21 (8.9)	33 (15.9)
Important other	47 (19.8)	46 (22.1)

*P < 0.0001 (chi-squared test).
†Infections requiring hospitalization.
‡P < 0.05 (chi-squared test).
§Includes myocardial infarction, heart failure, percutaneous transluminal coronary angioplasty, and atrial fibrillation.

hyperlipidemia, diabetes mellitus, a minimization of adverse events specific to steroids (osteoporosis, fractures, cataracts, skin bruising, Cushing's syndrome, serious infections and gastrointestinal events) or as a consequence of reduced overall immunosuppressive load, and finally improvement of patient adherence due to a decreasing pill number [17]. Interestingly, we found less bone fractures in the tacrolimus group of our study, possibly due to less steroid use. However, most reviews and meta-analyses have demonstrated that corticosteroid avoidance or early corticosteroid withdrawal after renal transplantation were associated with higher acute rejection rates, that, however, did not negatively affect patient or renal allograft survival especially in renal transplant recipients on a combined tacrolimus/MMF-based baseline immunosuppression [18–22]. Furthermore, a very large prospective trial of corticosteroid withdrawal ≥6 months post-transplant in renal transplant recipients reported significantly improved patient and renal allograft survival [23]. In addition, cardiovascular risk factors were significantly improved, whereas acute rejection rates in comparison with corticosteroid continuation in retrospectively matched renal transplant recipients were not different [23].

In our trial, kidney function was similar in both treatment arms. In a 5-year multicenter trial serum creatinine concentrations were significantly higher in renal transplant recipients treated with ciclosporin in comparison with tacrolimus treatment [8]. In a Cochrane meta-analysis of 4102 renal transplant recipients [24], renal allograft survival and renal transplant function were superior with tacrolimus in comparison with cyclosporin, thereby confirming and extending the results of a number of randomized studies [1,4,5,8,12,13]. These findings have been confirmed in the very large ELITE Symphony study at 1 and 3 years post-transplant [6,7].

Taking the above reports into account, we had expected that renal allograft function might be better in the tacrolimus group. However, this hypothesis was not supported by our data. Our results did show that renal function at 7 years was similar with tacrolimus versus CsA-ME [serum creatinine 139 (SD ± 55.9) vs. 147 (SD ± 70.7) μmol/l, estimated creatinine clearance (Cockroft–Gault) 63.5 (SD ± 20.8) ml/min vs. 58.4 (SD ± 22.1) ml/min]. We speculate that relatively more patients with inferior renal outcome in the CsA-ME versus tacrolimus group did not contribute to renal function parameters (only 72.1% CsA-ME patients vs. 76.8% of Tac patients, that contributed 7-year follow-up data also contributed serum creatinine concentrations). Moreover, average tacrolimus whole blood trough levels ranging around 12.5 (SD ± 3.8), 10.1 (SD ± 3.4) ng/ml, 8.7 (SD ± 2.5) ng/ml, 8.3 (SD ± 2.7) ng/ml, and 7.0 (SD ± 2.1) ng/ml at 0.5, 1, 2, 3, and 7 years post-transplant, that would be judged as being comparably very high by most renal transplant programs today, may have contributed by way of its nephrotoxic potential to this similar renal allograft function at 7 years.

At 7 years of follow-up, we found no more hypercholesterolemia in the CsA-ME treatment group presumably due to a higher use of antihyperlipidemics and lower cyclosporine doses in that group of long-term transplanted patients. At 6 months post-transplant, we had reported a significant difference in cardiovascular risk factors and estimated cardiovascular risk favouring the tacrolimus treatment group (with the exception of post-transplant diabetes, that was more frequent with tacrolimus) [25]. Accordingly, in the present analysis less major cardiovascular events with tacrolimus were found. Another study reported significant differences between tacrolimus and CsA-ME regarding cardiovascular risk factors after 3 years [5]. After 5 years of follow-up, a comparative US trial reported significantly more use of antihypertensives and antihyperlipidemics with ciclosporin compared with tacrolimus [8]. Interestingly, in the present European study in renal transplant patients at 7 years post-transplant both use of insulin and of oral antihyperglycemics as well as plasma glucose levels were similar between tacrolimus and CsA-ME arms. When taking into account the known higher diabetogenic risk associated with tacrolimus in comparison with the diabetogenic risk associated with cyclosporine use, the lack of differences in the number of renal transplant recipients needing antidiabetic treatment could be due to the high rate of tacrolimus patients with steroids withdrawn, the comparably low corticosteroid dose in the renal transplant recipients continuing corticosteroid treatment, the, at least in comparison with early studies, relatively lower tacrolimus trough concentrations at 7 years, and the well-recognized low risk for PTDM in Caucasians [26]. When our 7-year follow-up study was initiated, definition of PTDM according to the 2003 International Consensus Guidelines [26] was not part of renal transplantation studies. Therefore, PTDM according to current ADA/WHO guidelines was not assessed in our follow-up study.

An obvious limitation of our study is that the follow-up study cohort was restricted to approximately 80% of the original ITT cohort, as seven of the 50 transplant centers of the main study did not participate in the present investigator-initiated follow–up study. However, the percentage of study participants that were available for follow-up analysis is in the same range were available in other long-term trials [1,7,8]. Furthermore, our findings in the present follow-up trial may well be considered as representative for the whole trial, because the 43 participating transplant centers provided nearly complete follow-up data. In consequence, the results obtained by our investigator-initiated follow-up are considered as valid and most probably do not introduce undue bias.

In conclusion, tacrolimus treatment was more effective at year 7 as demonstrated by a significantly higher percentage of patients free from combined endpoint (BPAR, renal allograft loss, and patient death) in this treatment arm. From a clinical view, treatment with tacrolimus was better, as more patients were able to continue randomized treatment or tacrolimus monotherapy, fewer additional immunosuppressives were used in this treatment arm, and renal transplant recipients treated with tacrolimus had less clinically relevant side effects (i.e., cosmetic, fractures, and major cardiovascular events), and less use of antihyperlipidemics.

Authorship

BKK: prepared the first draft of the article. All authors contributed to the conception/design of the work, to acquisition of data and/or analysis of data, to interpretation of data, to writing or revising of the work, provided important intellectual content, finally approved and are accountable for the work. The sponsor had no role in design or conduct of the investigator-initiated follow-up trial, in collection, management, analysis, and interpretation of the data, and in drafting, review, and approval and decision to submit the manuscript for publication.

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Data S1. Complete list of investigators.

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