Efficacy and safety of tacrolimus compared with cyclosporin A microemulsion in renal transplantation: 2 year follow-up results

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Abstract

Background. Comparison studies of calcineurin inhibitors as cornerstone immunosuppressants in renal transplantation have demonstrated that tacrolimus consistently reduces acute rejection rates and, in some studies, also improves long-term renal outcome in comparison to cyclosporin A (CsA). The aim of the present 2 year follow-up of the European Tacrolimus vs Cyclosporin A Microemulsion Renal Transplantation Study was to investigate long-term clinical outcome in terms of rate of acute rejection, graft and patient survival and graft function.

Methods. The European Tacrolimus vs Cyclosporin A Microemulsion Renal Transplantation Study was a randomized, comparative 6 month trial of the calcineurin inhibitors tacrolimus and CsA in combination with both azathioprine and steroids. The intent-to-treat population (ITT) consisted of 286 patients in the tacrolimus arm and 271 in the CsA microemulsion (CsA-ME) arm. Whereas whole blood level targets were 10–20 and 5–15 ng/ml for tacrolimus and 100–400 and 100–200 ng/ml for CsA during months 0–3 and 4–6, respectively, during the investigator-driven follow-up after termination of the main study (months 7–24) no specific calcineurin inhibitor target levels were required. Follow-up data were collected at 2 years post-transplantation from 237 (82.9% of the ITT population) patients who received tacrolimus and 222 (81.9% of the ITT population) patients who received CsA-ME.

Results. Calculated on ITT populations, mortality (2.0% vs 3.3%; $P<0.05$ in Kaplan–Meier analysis) was lower, but rate of graft loss (9.3% vs 11.2%; $P=0.12$ in Kaplan–Meier analysis) was not significantly different after 2 years with tacrolimus- vs CsA-ME-based immunosuppression. Biopsy-proven acute rejection was significantly lower (19.6%) with tacrolimus than with CsA-ME (37.3%) during months 0–6 ($P<0.0001$), but was not significantly different during months 7–12 and 13–24 of follow-up (1.7% and 0.8% with tacrolimus and 4.7% and 0.9% with CsA-ME, respectively). A composite endpoint consisting of graft loss, patient death and biopsy-proven acute rejection occurred significantly more frequently in CsA-ME patients than in tacrolimus patients (42.8% vs 25.9%; $P<0.001$) during 24 months follow-up. Renal function 2 years post-transplant, measured by serum creatinine concentrations, was significantly better in tacrolimus-based compared with CsA-ME-based immunosuppression (136.9 vs 161.6 μmol/l; $P<0.01$). Cornerstone immunosuppression remained unchanged

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The principal investigators for the Study Group are listed in the ‘Acknowledgements’.
in 82.5% and 66.2% of patients treated with tacrolimus and CsA-ME, respectively. At 2 years, more patients in the tacrolimus arm were off steroids and received calcineurin inhibitor monotherapy, and fewer tacrolimus patients remained on a triple immunosuppressive regimen. The cardiovascular risk profile was affected favourably in the tacrolimus arm, with lower cholesterol and triglyceride concentrations (despite less use of cholesterol-lowering drugs); no significant difference in requirement for anti-diabetic medication was noted.

**Conclusions.** The 2 year study results confirm that tacrolimus is a highly efficacious cornerstone immunosuppressant in kidney transplantation. Tacrolimus-based immunosuppression may induce long-term benefits with regard to graft function and graft survival. The overall side-effect profile is considered to be favourable.

**Keywords:** acute rejection; cyclosporin A microemulsion; long-term follow-up; renal function; renal transplantation; tacrolimus

**Introduction**

Calcineurin inhibitors are considered the mainstay of immunosuppression in renal transplantation [1]. Cyclosporin A (CsA) and tacrolimus are currently the most widely used baseline immunosuppressants for prevention of acute rejection following kidney transplantation. Two large, randomized, multicentre studies conducted in Europe and the US demonstrated that the incidence of acute rejection was significantly less in 508 renal transplant recipients receiving tacrolimus-based immunosuppression compared with 355 receiving CsA-based immunosuppression [2,3]. Projected graft half-life was longer and chronic rejection less frequent with tacrolimus-based immunosuppression at 5 year follow-up [2]. Furthermore, renal function better after 5 years in patients receiving tacrolimus-based immunosuppression compared with CsA-based immunosuppression [3]. The availability of a microemulsified formulation of CsA has replaced the standard formulation. The objective of this study was to determine whether the superior efficacy of tacrolimus in preventing acute graft rejection was still valid when compared with the CsA microemulsion (CsA-ME) formulation. The 6- and 12-month data have been presented previously and demonstrated a halving of biopsy-proven and steroid-resistant acute rejection rates with tacrolimus vs CsA-ME treatment [4,5]. In addition to rate and severity of acute rejection, graft survival, longer-term graft function and patient survival are focuses of medical therapy after renal transplantation. Studies have demonstrated that severe and recurrent acute rejections as well as late and vascular-type acute rejections have a significant adverse impact on graft survival and chronic allograft nephropathy [6–8]. Tacrolimus-based immunosuppression positively influences long-term graft function and survival. In support of this assumption, two recent randomized, controlled trials demonstrated less upregulation of profibrotic growth factors and less interstitial fibrosis with tacrolimus treatment [8,9]. In healthy subjects, CsA is known to decrease glomerular filtration rate (GFR) and renal blood flow and increase renal vascular resistance, whereas tacrolimus does not [10]. In renal transplant patients, long-term treatment with tacrolimus resulted in a lower renal resistance index and less need for antihypertensives compared with CsA [11]. Recently, long-term data from the Cardiff Tacrolimus vs Cyclosporin Kidney Transplant Study (randomization of 232 patients to tacrolimus or CsA microemulsion cornerstone immunotherapy) demonstrated higher 6 year graft survival, longer estimated graft half-life and significantly better renal function (GFR) with tacrolimus [12]. Finally, several studies have documented lower blood pressure and serum cholesterol levels during tacrolimus as opposed to CsA treatment in renal transplant recipients, conceivably resulting in a decreased cardiovascular risk [13,14].

**Subjects and methods**

This randomized, open study was conducted in 50 transplant centres in seven European countries. Some 557 patients, aged 18–60 years, with end-stage renal disease were administered either tacrolimus (n = 286) or CsA-ME (n = 271) combined with azathioprine and corticosteroids. Study duration was 6 months, after which patients were followed-up for an additional 18 months. The primary endpoint of the main study was the incidence and time to onset of first acute rejection episode. Secondary efficacy endpoints included patient and graft survival, severity of biopsy-proven acute rejection (according to the Banff 93 grading system) and the incidence and time to corticosteroid-resistant acute rejection [4].

The tacrolimus dose (initial oral dose 0.3 mg/kg administered within 24 h of transplantation) was adjusted to maintain target whole blood trough levels of 10–20 ng/ml during the first 3 months and 5–15 ng/ml between months 4 and 6. CsA-ME treatment started on day 0 with an oral dose of 4–5 mg/kg twice daily. Target whole blood trough levels of CsA-ME 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 comprised methylprednisolone boluses (day 0: 500 mg; day 1: 125 mg) followed by a rapid prednisone taper from 20 mg (day 2) to 5 mg (day 43 and thereafter). During the investigator-driven follow-up after termination of the main study (months 7–24) no specific calcineurin inhibitor target levels were required. Adverse events, laboratory parameters and renal function (serum creatinine) were recorded throughout the study. The intent-to-treat (ITT) population was used for all analyses of efficacy and safety. Statistical analysis was conducted with Pearson's χ², Fisher's exact test, Student's t-test, Wilcoxon rank sum test or Kaplan–Meier survival procedures where appropriate.
Results

Demographic and baseline characteristics were similar between the two treatment groups (Table 1) [4]. Of the original 557 patients randomized to treatment, 237 (82.9% of 286) patients in the tacrolimus treatment group and 222 (81.9% of 271) patients in the CsA-ME group were assessed at 2 year follow-up (Table 1). Thirty-six of 50 centres participated in this 2 year follow-up. In the tacrolimus arm, three patients died at 0–12 months and one at 13–24 months [4 (1.4%) deaths]. In the CsA-ME group, six patients died at months 0–12 and one at 13–24 months [7 (2.6%) deaths]. In the tacrolimus treatment group, 18 grafts were lost between months 0 and 12 and four between months 13 and 24, totalling 22 (7.7%). Twenty-four grafts were lost in the CsA-ME treatment group between months 0 and 12 and three between months 7 and 24, totalling 27 (10.0%). Calculated on ITT populations, overall mortality (2.0% vs 3.3%; \(P<0.05\) in Kaplan–Meier analysis) was lower, but overall rate of graft loss (9.3% vs 11.2%; \(P=0.12\) in Kaplan–Meier analysis) was not significantly different after 2 years with tacrolimus- vs CsA-ME-based immunosuppression (Figures 1 and 2).

Biopsy-proven acute rejection was significantly lower (19.6%) with tacrolimus than with CsA-ME (37.3%) during months 0–6 \((P<0.0001)\), but was not significantly different during months 7–12 and 13–24 of follow-up (1.7% and 0.8% with tacrolimus and 4.7% and 0.9% with CsA-ME) (Table 2). During months 13–24, biopsy-proven acute rejection was diagnosed in two tacrolimus and two CsA-ME graft recipients. None of the tacrolimus-treated patients compared with one of the CsA-ME patients developed corticosteroid-resistant rejection between months 13 and 24. Two tacrolimus and one CsA-ME patients had a Banff I rejection and one CsA-ME patient had a Banff III rejection. Two tacrolimus and three CsA-ME patients were diagnosed with biopsy-proven chronic rejection at months 0–6, no cases were reported at months 7–12 and two tacrolimus and four CsA-ME patients were diagnosed at months 13–24.

A composite endpoint consisting of graft loss, patient death and biopsy-proven acute rejection occurred significantly more frequently in CsA-ME patients than in tacrolimus patients (42.8% with CsA-ME and 25.9% with tacrolimus; \(P<0.001\)) during 24 months follow-up.

Significantly more patients had been switched from CsA-ME treatment to tacrolimus between months 0 and 6 due to lack of efficacy or adverse events (10% vs 0.3%; \(P<0.0001\)) [4]. By month 24, 20.3% of ITT patients receiving CsA-ME (\(n=271\)) were switched to tacrolimus compared with 2.5% of tacrolimus-treated patients (\(n=286\)) who were switched to CsA-ME (Table 3). Of patients remaining in their original treatment group at 24 months, 0.9% of CsA-ME and 14.8% of tacrolimus patients received monotherapy. Fewer non-switched tacrolimus patients (24.5%) than non-switched CsA-ME patients (32%) were on a triple immunosuppressive regimen and fewer (80.6% vs 91.0%) remained on steroids at 24 months follow-up (mean dose: 4.8 vs 5.5 mg prednisolone).

Mean serum creatinine concentrations were 146.4 \(\mu\)mol/l in the tacrolimus group and 158.6 \(\mu\)mol/l.

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Table 1. Demographic data of the 24-month follow-up patients

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Tacrolimus ((n=237))</th>
<th>CsA-ME ((n=222))</th>
<th>Total ((n=459))</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>170 (71.7%)</td>
<td>138 (62.2%)</td>
<td>308 (67.1%)</td>
</tr>
<tr>
<td>Female</td>
<td>67 (28.3%)</td>
<td>84 (37.8%)</td>
<td>151 (33%)</td>
</tr>
<tr>
<td>Caucasian</td>
<td>234 (98.7%)</td>
<td>222 (100%)</td>
<td>456 (99.4%)</td>
</tr>
<tr>
<td>Oriental</td>
<td>3 (1.3%)</td>
<td>0</td>
<td>3 (0.7%)</td>
</tr>
<tr>
<td>Age (years)</td>
<td>43</td>
<td>43</td>
<td>43</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>169</td>
<td>168</td>
<td>169</td>
</tr>
<tr>
<td>Body weight (kg)</td>
<td>74</td>
<td>74</td>
<td>74</td>
</tr>
</tbody>
</table>

Data are presented as \(n\) (%) or means.

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![Estimated Patient Survival Rate (Kaplan–Meier Method)](image1)

**Fig. 1.** Patient survival at 2 years of follow-up.

![Estimated Graft Survival Rate (Kaplan–Meier Method)](image2)

**Fig. 2.** Graft survival at 2 years of follow-up.
in the CsA group by month 12. Mean serum creatinine concentrations were 136.9 ± 74.4 µmol/l (n = 227) in the tacrolimus group and 161.6 ± 129.1 µmol/l (n = 207) in the CsA-ME group at 24 months (P < 0.01) (Figure 3). Creatinine clearance according to the Cockcroft–Gault formula differed accordingly, with 68.9 ± 23.2 ml/min (n = 213) under tacrolimus compared with 61.8 ± 23.2 ml/min (n = 196) under CsA-ME treatment. During week 1, the mean oral dose of tacrolimus and CsA-ME was 0.22 and 7.20 mg/kg/day, respectively, and decreased to 0.10 and 0.09 mg/kg/day and 3.16 and 2.93 mg/kg/day by months 12 and 24. Mean whole blood trough levels during week 1 were 17.9 ng/ml (tacrolimus) and 277.9 ng/ml (CsA-ME) and decreased to 10.1 and 159.0 ng/ml and 8.74 and 149.5 ng/ml by months 12 and 24, respectively.

No significant difference in blood pressure was found between either group at 2 years [135.2 ± 17.5/82.3 ± 9.6 mmHg (n = 218) vs 135.7 ± 16.4/81.4 ± 9.9 mmHg (n = 203)]. At month 24 the numbers on antihypertensive (78.9% vs 72.3%; number of antihypertensives 2.2 vs 2.0) and diuretic (17.6% vs 13.5%) medication was not significantly different in patients in the CsA-ME group compared with patients in the tacrolimus group. Cholesterol and triglyceride levels were significantly lower at 2 years in the tacrolimus arm: cholesterol, 5.24 ± 1.04 (n = 198) vs 5.49 ± 1.04 mmol/l (n = 175) (P < 0.01); triglycerides, 1.59 ± 0.86 (n = 190) vs 1.75 ± 1.03 mmol/l (n = 164) (P < 0.05). At month 24, more patients in the CsA-ME treatment group required antihyperlipidaemic (32.0% vs 16.0%; P < 0.001) medication compared with patients in the tacrolimus group. Twenty (8.5%) tacrolimus-treated patients received insulin at month 24 compared with 17 (7.8%) patients in the CsA treatment group; 2.5% vs 2.3% of patients required oral antihyperglycaemic agents. New-onset diabetes mellitus was diagnosed at months 0–24 in eight tacrolimus patients (3.6%) and four CsA-ME patients (1.9%) (not statistically different). Cosmetic adverse events (gingival hyperplasia and hirsutism) were observed more often in the CsA-ME treatment group as compared with the tacrolimus group (Table 4).

**Discussion**

This is the first major study in kidney transplantation that compares the efficacy and safety of a tacrolimus-based regimen with the microemulsion formulation of CsA. At 6 months, tacrolimus-treated patients had significantly less biopsy-proven acute rejection; the superior efficacy of the tacrolimus-based regimen in preventing acute rejection was maintained 2 years post-transplantation. Late acute rejections in the tacrolimus group tended to be less frequent and had a lower histological grade than in the CsA-ME group.
group. A composite endpoint consisting of graft loss, patient death and biopsy-proven acute rejection was reached significantly less frequently with a tacrolimus-based regimen at 2 years post-transplantation.

The higher effectiveness of tacrolimus is substantiated further by the significant number of patients who were switched from CsA-ME to tacrolimus treatment because of lack of efficacy and adverse events (mostly treatment-resistant rejection). Regarding the use of steroids, more patients in the tacrolimus group were off steroids and on monotherapy as compared with the CsA-ME group at 2 years. Reducing the incidence of acute rejection is paramount to attaining improved outcomes as it contributes to a decrease in the need for supplemental medications and rehospitalizations, thereby reducing healthcare costs and complicated patient management. Of even greater importance are the probable beneficial effects on long-term graft function and graft survival attainable when the episodes of severe, recurrent or late acute rejections are reduced by a specific immunosuppressive regimen [6–8].

Another important finding of the present study was that serum creatinine concentrations were significantly lower at the 2 year follow-up in the tacrolimus group compared with the CsA-ME group. This finding may be due to both less (and less severe) acute allograft rejection with tacrolimus and to less renal vasoconstriction/calcineurin-inhibitor toxicity [10,11]. In line with these findings, trends for less chronic allograft nephropathy and better patient and graft survival were observed with tacrolimus therapy in the present trial. These findings correlate with both the 5 year results of the European and the US trials comparing tacrolimus with the standard formulation of CsA, demonstrating improved graft function and graft survival and less chronic allograft nephropathy [2,3]. Further, a recent study of 40,963 US Renal Data System (USRDS) first kidney only transplant recipients ±2 years post-transplant demonstrated a significantly slower decline in GFR in tacrolimus- vs CsA-ME-treated patients [15].

Similar to the results in this study, lower mean cholesterol and triglyceride levels in the Cardiff Study [12] indicated a more favourable cardiovascular risk profile in patients treated with tacrolimus vs those who received CsA-ME. However, the present trial is not adequately powered to study the effects of different calcineurin inhibitors on cardiovascular endpoints. The high efficacy of tacrolimus allowed reduction or discontinuation of steroids and the initiation of monotherapy, thereby contributing to a beneficial impact on cardiovascular risk factors [13]. In line with these findings, data obtained in 11,659 first renal transplant recipients from the USRDS and Medicare suggest that tacrolimus use, despite more post-transplant diabetes mellitus, goes along with improved patient (and graft) survival [16]. The safety profile of the tacrolimus regimen indicated further advantages with respect to cosmetic side effects.

Potential limitations of the present analysis are firstly, that our follow-up is limited to only 82.9% or 81.9% of patients of the original cohort, since 14 (of 50) centres did not participate in this investigator-driven follow-up. Nevertheless, we think that our analysis is valid since patients had been randomized to tacrolimus or CsA-ME within every participating transplant centre and the follow-up within each participating centre was complete. Secondly, the rate of acute rejections may be considered high in the present study; however, it has to be taken into account that azathioprine [and not mycophenolate mofetil (MMF)] and a rapid steroid-tapering protocol was used in the triple immunosuppressive drug regimens. However, this regimen allows better judgement of the respective immunosuppressive properties of each calcineurin inhibitor than in a regimen with a very high immunosuppressive background therapy, i.e. a combination treatment with MMF ± additional antibody induction. Thirdly, it could be argued that C2 monitoring of CsA exposure might have yielded superior results; however, when the present trial was planned and performed in 1998/1999, C2 monitoring could by no means be considered as standard. Furthermore, despite highly suggestive pharmacokinetic considerations and its widespread use, no controlled, prospective trial comparing C2 vs C0 monitoring has ever shown improved patient outcomes in renal transplant recipients with C2 monitoring [17,18].

In conclusion, these data are consistent with previously published observations and confirm that tacrolimus is a highly efficacious baseline immunosuppressant for patients undergoing kidney transplantation. Tacrolimus-based immunosuppression may promote long-term benefits with regard to graft function and graft survival.

Acknowledgements. We thank the following investigators for their contribution to this study: R. Margreiter, Landeskrankenhaus, Innsbruck; K.H. Dietl, Westfälische Wilhelms Universität, Münster; H. Sperschneider, KKH Nierenzentrum, Jena; D. del Castillo, Hospital Reina Sofia, Córdoba; J. Ortuño and J. Pascual, Hospital Ramón y Cajal, Madrid; C. Olbricht, Katharinen hospital, Stuttgart; B. Krämer, M. Kammerl and B. Krüger, Universität Regensburg; H. Köhler and U. Sester, Universitätssklinik des Saarlandes, Homburg; F. Mühlbacher, Allgemeines Krankenhaus Wien; U. Kunzendorf and I. Hauser, Med. Klinikum IV, Erlangen; H. Stumvoll, KH Elisabethinen Linz; C. Ponticelli, Ospedale

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**Table 4. Adverse events occurring between months 13 and 24**

<table>
<thead>
<tr>
<th></th>
<th>Tacrolimus (n = 237)</th>
<th>CsA-ME (n = 222)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Malignancies</td>
<td>3 (1.3%)</td>
<td>1 (0.5%)</td>
</tr>
<tr>
<td>Cosmetic</td>
<td>7 (3.0%)</td>
<td>31 (14%)</td>
</tr>
<tr>
<td>Severe infections</td>
<td>9 (3.8%)</td>
<td>9 (4.1%)</td>
</tr>
<tr>
<td>Fractures, bone disease</td>
<td>5 (2.1%)</td>
<td>12 (5.4%)</td>
</tr>
<tr>
<td>Cardiovascular</td>
<td>6 (2.5%)</td>
<td>1 (0.5%)</td>
</tr>
</tbody>
</table>

*P < 0.001.

For example, myocardial infarction, heart failure, percutaneous transluminal coronary angioplasty and atrial fibrillation.
Conflict of interest statement. The main study and the investigator-driven long-term follow-up was sponsored by Fujisawa. BKK has participated in clinical trials sponsored by Fujisawa, Novartis, and Wyeth, has received lecture fees from Fujisawa, Novartis, and Wyeth, has obtained research grants from Fujisawa, Novartis, and Wyeth, has received lecture fees from Fujisawa, Novartis, and Wyeth, has participated in clinical trials sponsored by Fujisawa, Novartis, and Wyeth, has obtained research grants from Fujisawa and Wyeth, has received lecture fees from Fujisawa, Novartis, and Wyeth, has participated in clinical trials sponsored by Fujisawa. BKK has driven long-term follow-up was sponsored by Fujisawa. BKK has driven long-term follow-up was sponsored by Fujisawa. BKK has driven long-term follow-up was sponsored by Fujisawa. BKK has driven long-term follow-up was sponsored by Fujisawa. BKK has driven long-term follow-up was sponsored by Fujisawa. BKK has driven long-term follow-up was sponsored by Fujisawa. BKK has driven long-term follow-up was sponsored by Fujisawa. BKK has driven long-term follow-up was sponsored by Fujisawa. BKK has driven long-term follow-up was sponsored by Fujisawa. BKK has driven long-term follow-up was sponsored by Fujisawa. BKK has driven long-term follow-up was sponsored by Fujisawa. BKK has driven long-term follow-up was sponsored by Fujisawa. BKK has driven long-term follow-up was sponsored by Fujisawa. BKK has driven long-term follow-up was sponsored by Fujisawa. BKK has driven long-term follow-up was sponsored by Fujisawa. BKK has driven long-term follow-up was sponsored by Fujisawa.

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Received for publication: 23.9.04
Accepted in revised form: 19.1.05