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Efficacy and safety of tacrolimus compared with cyclosporin microemulsion in primary SPK transplantation: 3-year results of the Euro-SPK 001 trial

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Abstract

Background. Single-centre and retrospective studies suggest superiority of tacrolimus over cyclosporin as cornerstone immunosuppressive therapy for simultaneous pancreas–kidney (SPK) transplantation. This open-label, multicentre trial compared the efficacy and safety of tacrolimus with cyclosporin microemulsion (ME) in diabetic patients with end-stage renal disease undergoing their first cadaveric SPK transplantation. The 3-year results are reported.

Methods. Patients were recruited from 10 centres in Europe and one centre in Israel: 103 were randomized to receive tacrolimus (initial dose: 0.2 mg/kg/day p.o.) and 102 to cyclosporin-ME (7 mg/kg/day p.o.). All patients received concomitant rabbit anti-T-cell globulin induction, mycophenolate mofetil (MMF) and short-term corticosteroids.

Results. Fewer patients receiving tacrolimus (36.9%) than cyclosporin-ME (57.8%) were discontinued from treatment ($P = 0.003$). The initial episodes of biopsy-proven rejection were moderate or severe in just one out of 31 (3%) tacrolimus-treated patients compared with 11 out of 39 (28%) patients receiving cyclosporin-ME ($P = 0.009$). While 3-year patient and kidney survival rates were similar in the two treatment groups, pancreas survival was superior with tacrolimus (89.2 *vs* 72.4%; $P = 0.002$). Thrombosis resulted in pancreas graft loss in 10 patients receiving cyclosporin-ME and in only two treated with tacrolimus ($P = 0.02$). Overall adverse event frequency was similar in both groups, but MMF intolerance was more frequent with tacrolimus and hyperlipidaemia more frequent with cyclosporin-ME.

Conclusions. In this 3-year study, tacrolimus was more effective than cyclosporin-ME in preventing moderate or severe kidney or pancreas rejection after SPK transplantation. It also provided superior pancreas survival and reduced the risk of pancreas graft thrombosis.

Keywords: cyclosporin microemulsion; immunosuppression; rejection; simultaneous pancreas–kidney transplantation; tacrolimus

Introduction

Simultaneous pancreas–kidney (SPK) transplantation is a recommended treatment option for type 1 diabetic patients suffering from end-stage kidney disease [1]. Independence from exogenous insulin together with long-term normoglycaemia, without the risk of severe hypoglycaemia, not only improves quality of life but may also stabilize, or even reverse, the microvascular complications of diabetes and thereby ameliorate cardiovascular risk factors [2]. The procedure has also been shown to improve long-term survival compared with that achieved with kidney transplantation alone [3–5]. Major factors contributing to the success of SPK transplantation include improvements in surgical technique and the provision of effective immunosuppressive strategies heralded by the introduction of the calcineurin inhibitors [2,6,7].

Data from single-centre studies and retrospective analyses comparing tacrolimus and cyclosporin microemulsion (cyclosporin-ME) in the SPK clinical setting suggest superior results with the use of

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tacrolimus [8–11]. However, these findings have not been confirmed by data from large, prospective, randomized, multicentre studies.

We report the results of an international multicentre trial designed to compare prospectively the efficacy and safety of tacrolimus with those of cyclosporin-ME over a follow-up period of 3 years in type 1 diabetic patients with end-stage kidney disease undergoing their first cadaveric SPK transplantation. The interim 1-year results of this study have been reported previously [12].

Patients and methods

The study design has been published previously in the 1-year interim report [12].

Patients, trial design and immunosuppressive therapy

Patients aged 18–55 years with type 1 diabetes who were C-peptide negative with end-stage kidney disease and were suitable candidates for primary SPK transplantation were eligible for inclusion in the study. A whole-pancreas technique with either enteric or bladder drainage was used. Cadaveric donors aged 50 years or younger were accepted.

The study was of an open-label, prospective, parallel-group design. Randomization (1:1) to either tacrolimus (Prograf®) or cyclosporin-ME (Neoral®) immunosuppressive therapy was performed centrally. All patients received adjunctive medication consisting of mycophenolate mofetil (MMF; CellCept®), short-term corticosteroids and rabbit anti-T-cell globulin [(rATG) ATG Fresenius or Thymoglobulin®].

Therapy with calcineurin inhibitors was started orally or, if necessary, via a nasogastric tube within 6 h of skin closure. The initial dose of tacrolimus was 0.1 mg/kg twice daily, with subsequent dosage adjustments given to achieve whole-blood trough levels of 8–15 ng/ml by day 5. Cyclosporin-ME was administered at an initial daily dose of 7 mg/kg in two divided doses, adjusted to maintain whole-blood trough levels between 150 and 250 ng/ml by day 5. After month 6, target levels of tacrolimus and cyclosporin-ME were reduced to 5–10 and 100–200 ng/ml, respectively. Trough blood concentrations were measured using the IMx Tacrolimus II assay for tacrolimus and a monoclonal antibody assay for cyclosporin.

MMF was administered at an initial dose of 2–3 g/day, with subsequent dosage adjustments based on tolerability and adverse effects. Therapy with rATG was started perioperatively, with the first dose administered before unclamping the first transplanted organ, followed by three daily post-operative doses of rATG (ATG Fresenius 4 mg/kg/day or Thymoglobulin 1.25 mg/kg/day). The choice of the rATG and the corticosteroid regimens varied according to standard practices at each study centre. However, in all centres, corticosteroid therapy was gradually tapered, with the aim of complete withdrawal by month 6. Rejection treatment as well as prophylactic antibiotic and anti-cytomegalovirus (CMV) therapy were administered according to routine procedures.

The study was approved by local ethics committees and was undertaken in accordance with the Declaration of Helsinki. Written informed consent was obtained from all participants.

Efficacy and safety assessments

The primary efficacy end-points were the incidence of biopsy-proven acute rejection of either the pancreas or kidney and the incidence of treatment failure for any reason. In suspected cases of pancreas or kidney graft rejection, biopsy samples were taken and analysed by a local histopathologist. A percutaneous renal biopsy was undertaken in all cases prior to initiation of anti-rejection therapy. Renal biopsies were graded as 'borderline', 'mild', 'moderate' or 'severe' in accordance with the 1997 Banff classification [13]. Pancreas biopsies were rated according to the Drachenberg scale [14]. If renal or pancreas biopsies were not available, clinically suspected and treated rejection was recorded separately. Treatment failure was defined according to the following guidelines: switch to another immunosuppressive drug; permanent discontinuation of a drug (except corticosteroids); withdrawal for adverse events; graft loss (pancreatic or renal transplantectomy); delayed kidney graft function requiring dialysis for >1 month; functional graft loss of kidney or pancreas; and death of the patient. Functional kidney graft loss was defined as a return to dialysis and functional pancreas graft loss as a need for exogenous insulin.

Secondary efficacy end-points included: 3-year patient and graft survival; time to the first rejection episode; the histological grade of rejection; incidence of rejection leading to graft loss; the cumulative dose of corticosteroids administered; and the number and duration of hospitalizations. Other assessments included kidney graft function, as assessed by the measurements of serum creatinine and the calculated glomerular filtration rate (Cockcroft–Gault formula), and pancreas graft function, assessed by measurements of fasting blood glucose levels, fasting C-peptide and glycosylated haemoglobin (HbA_{1C}). Routine methods of haematology and clinical chemistry were applied in each centre.

Infection, cancer, surgical events, hospitalization, and cerebrovascular and cardiovascular complications were recorded until 3 years follow-up, even if patients were withdrawn from the study.

Statistical analysis

The planned sample size was 200 patients using 1:1 randomization. The intent-to-treat population, used for analyses of efficacy and safety, included all randomized patients who underwent transplantation and received at least one dose of study medication. χ^2 and Fisher's exact tests were used to compare categorical variables. The Mann–Whitney U-test was used to compare continuous variables. Survival rates were obtained using the Kaplan–Meier method and compared by using the log-rank test. For all statistical tests, P-values of <0.05 were considered to be statistically significant. Mean values are given with SDs.

Results

Patient disposition

Between May 1998 and September 2000, 127 male and 78 female patients (aged 18–55 years) from 11 centres in Europe and Israel were enrolled in the study. One hundred and three patients were assigned pre-operatively to receive tacrolimus treatment and

102 to receive cyclosporin-ME. The baseline characteristics of the patients in the two groups have been reported previously [12]. The two groups were comparable at baseline with respect to age, gender and sensitization. However, significantly more patients assigned to tacrolimus (91%) than cyclosporin-ME (81%; $P < 0.05$) were dialysis dependent prior to transplantation.

By the end of the 3-year follow-up, there were eight deaths: five in the tacrolimus group and three in the cyclosporin-ME group. There were significantly fewer withdrawals by patients treated with tacrolimus compared with cyclosporin-ME (36.9 *vs* 57.8%, respectively; $P = 0.003$). Reasons for withdrawal are listed in Table 1. A total of 22 patients withdrawn from treatment with cyclosporin-ME were switched to another immunosuppressive drug as a result of acute rejection, compared with only one patient withdrawn from tacrolimus for this reason. An additional eight patients receiving tacrolimus and 11 receiving cyclosporin-ME switched therapy for other reasons, namely glucose intolerance and non-immunological reasons (Table 1). MMF was withdrawn from 17 patients receiving tacrolimus and from two patients receiving cyclosporin-ME. Notably, two patients in the tacrolimus group were withdrawn from corticosteroids and MMF without experiencing any adverse event and thus received tacrolimus monotherapy for almost 3 years.

Immunosuppressive therapy

The time course of drug dosage and mean trough plasma levels are shown in Table 2. A significant difference between the two treatment groups was observed with respect to the number of patients requiring a change in their immunosuppressive therapy. While only nine (8.7%) patients in the tacrolimus group were switched to alternative immunosuppression (eight were converted to cyclosporin-ME and one was switched to sirolimus) during the 3-year follow-up, 36 (35.3%) patients in the cyclosporin-ME group were switched to tacrolimus therapy ($P < 0.0001$).

The mean daily dose of MMF decreased during the course of the study. At the end of the 3-year treatment period, the mean dose was 1.33 ± 0.46 g/day in the tacrolimus group and 1.54 ± 0.47 g/day in the cyclosporin-ME group ($P = 0.04$). The number of patients successfully withdrawn from corticosteroid therapy during the study was numerically higher in the tacrolimus group compared with the cyclosporin-ME group (54 *vs* 37, respectively). There was no significant difference with regard to rATG and corticosteroid usage in either treatment group.

Acute rejection

During the 3-year study, 41 patients (per protocol) in the tacrolimus group experienced 59 episodes of clinical or biopsy-proven rejection (1.44 episode/patient) and 51 patients in the cyclosporin-ME group experienced 73 episodes (1.43 episode/patient). The initial episodes of biopsy-proven rejection were moderate or severe in 11 out of 39 (28%) patients in the cyclosporin-ME group compared with just one out of 31 (3%) in the tacrolimus group, and this difference was statistically significant ($P = 0.009$). Analysis of all episodes of first and subsequent biopsy-proven rejections gave similar results: 17 out of 56 (30%) rejections were classified as moderate or severe in the cyclosporin-ME group compared with only one out of 38 (3%) in the tacrolimus group ($P = 0.0009$). The 3-year actuarial rejection-free survival rate was 54.2% in the tacrolimus group and 43.7% in the cyclosporin-ME group (Figure 1).

Table 1. Reasons for study withdrawal in tacrolimus- and cyclosporin microemulsion (ME)-treated simultaneous pancreas–kidney recipients

	Tacrolimus ($n = 103$)	Cyclosporin-ME ($n = 102$)
No. of withdrawals [*n* (%)]	38 (36.9)	59 (57.8)[a]
Death	2	0
Graft loss	9	22[b]
Switch for rejection	1	22
Switch for other causes	8	11
Glucose intolerance	4	2
Neurotoxicity	2	0
Thrombotic microangiopathy	1	0
Polyomavirus	1	0
Low cyclosporin absorption	0	3
Hypertrichosis	0	2
Unspecified cyclosporin toxicity	0	2
Gingival hyperplasia	0	1
Unknown	0	1
Mycophenolate mofetil withdrawal	17	2
Sepsis	0	1
Lost to follow-up	1	1

[a]$P = 0.003$ *vs* tacrolimus.
[b]Includes three switches after study withdrawal.

Table 2. Immunosuppressive therapy: mean doses and trough levels during the 3-year study

	Tacrolimus	Cyclosporin-ME
Mean ± SD trough level (ng/ml)		
Week 1	16.5 ± 8.1 ($n = 98$)	236 ± 109 ($n = 95$)
Month 3	12.5 ± 5.0 ($n = 86$)	185 ± 73 ($n = 59$)
Month 6	11.4 ± 4.2 ($n = 85$)	183 ± 87 ($n = 54$)
Year 1	10.4 ± 3.1 ($n = 77$)	171 ± 71 ($n = 47$)
Year 2	9.5 ± 4.2 ($n = 66$)	158 ± 53 ($n = 45$)
Year 3	9.3 ± 3.2 ($n = 54$)	146 ± 38 ($n = 34$)
Mean ± SD dose (mg/kg)[a]		
Day 1–7	0.14 ± 0.05 ($n = 99$)	6.8 ± 2.2 ($n = 99$)
Month 3	0.13 ± 0.05 ($n = 87$)	4.8 ± 1.5 ($n = 63$)
Month 6	0.11 ± 0.05 ($n = 78$)	4.5 ± 1.0 ($n = 52$)
Year 1	0.1 ± 0.04 ($n = 75$)	4.2 ± 1.1 ($n = 46$)
Year 2	0.1 ± 0.04 ($n = 66$)	3.9 ± 1.0 ($n = 44$)
Year 3	0.1 ± 0.04 ($n = 46$)	4.0 ± 1.0 ($n = 35$)

[a]mg/kg/day for day 1–7, thereafter mg/kg.

No significant differences were detected between the tacrolimus and the cyclosporin-ME groups with respect to the time of occurrence of the first rejection episode or the time to graft loss (Table 3). Among the patients who experienced no rejection at 3 years, there were significantly fewer grafts lost in the tacrolimus group than in the cyclosporin-ME group (7 *vs* 24%, respectively; $P = 0.02$). Of note, in the tacrolimus treatment group, there were significantly more graft losses among patients who had a rejection episode than among those who were free of rejection at 3 years (26 *vs* 7%, respectively; $P = 0.01$). This difference was not significant in the cyclosporin-ME group (38 *vs* 24%).

Patient and graft survival

Patient survival at 3 years post-transplantation was high in both treatment groups (95.1% with tacrolimus and 97.1% with cyclosporin-ME). Of the five deaths in the tacrolimus group, two occurred during the study and three after kidney and pancreas graft loss. In the cyclosporin-ME group, there were three deaths after study withdrawal.

Of note, pancreas graft survival at 3 years was significantly higher in the tacrolimus group (89.2%) than in the cyclosporin-ME group (72.4%; $P = 0.002$; Figure 2). As shown in Table 4, there was a significantly higher incidence of pancreas graft thrombosis in patients treated with cyclosporin-ME compared with that occurring among patients receiving tacrolimus-based therapy ($P = 0.02$). The thromboses occurred at a median time of 13 days, with only two cases occurring later than 1 month post-transplant (118 and 188 days). The difference between treatments was not attributable to a centre effect and was independent of the operative technique or the graft vessel extension.

No significant difference between the two treatment groups was found in terms of kidney graft survival (94.1% tacrolimus and 92.1% cyclosporin-ME). There were six cases of renal graft loss in the tacrolimus group compared with eight cases in the cyclosporin-ME group (Table 4). Two cases of death with a functioning graft were seen with both regimens.

Irrespective of the immunosuppressive regimen used, there were fewer deaths (three out of 157; 1.9%) among patients with functioning kidney and pancreas grafts than among patients who lost the kidney, the pancreas or both organs (five out of 45; 11.1%, $P = 0.01$).

Graft function

There was no significant difference between the two immunosuppressive regimens in terms of pancreas graft function among patients in the study at 3 years.

Table 3. Pancreas or kidney graft losses and rejection in tacrolimus- and cyclosporin microemulsion (ME)-treated simultaneous pancreas–kidney transplant patients

	Graft loss[a]	
	Tacrolimus ($n = 102$)[b]	Cyclosporin-ME ($n = 100$)[c]
First rejection episode [*n* (%)]		
0–6 months	9/41 (22)	18/49 (37)
6–12 months	2/3 (67)	2/3 (67)
>1 year	1/3 (33)	1/3 (33)
Total incidence of rejection [*n* (%)]	12/47 (26)[d]	21/55 (38)
Mean ± SD time to first rejection episode (days)	69 ± 149	65 ± 148
Mean ± SD time to graft loss (days)	412 ± 391	155 ± 214
No rejection at 3 years [*n* (%)]	4/55 (7)[d]	11/45 (24)
Mean ± SD time to graft loss (days)	202 ± 305	57 ± 67

[a]Including death with a functioning graft.
[b]One patient lost to follow-up during the study.
[c]One patient lost to follow-up during the study and one patient lost to follow-up after study withdrawal.
[d]$P < 0.05$ for tacrolimus *vs* cyclosporin-ME in patients with no rejection; for rejection *vs* no rejection in the tacrolimus group.

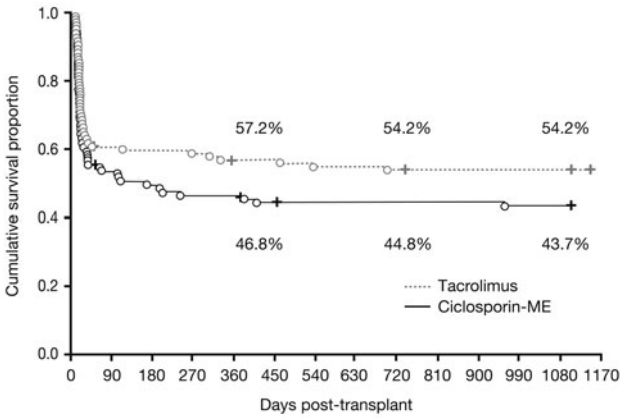

Fig. 1. Three-year actuarial rejection-free survival (Kaplan–Meier analysis) in simultaneous pancreas–kidney transplant patients receiving immunosuppression based on tacrolimus or cyclosporin microemulsion (ME). ○ = clinical and biopsy-proven rejection episode; + = censored.

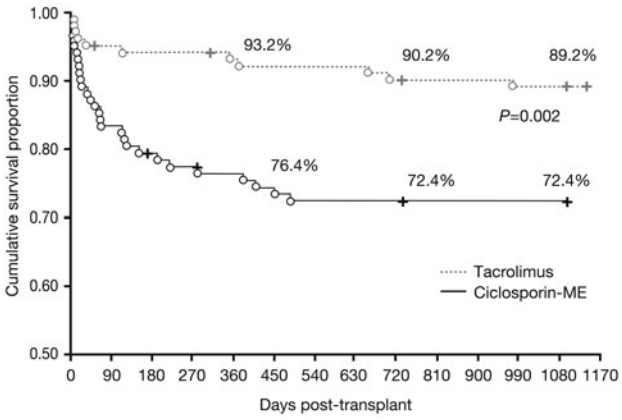

Fig. 2. Pancreas graft survival (Kaplan–Meier analysis) in the 3 years following simultaneous pancreas–kidney transplantation. At 3 years, pancreas survival was significantly higher in tacrolimus-compared with cyclosporin microemulsion-treated patients ($P = 0.002$). ○ = pancreas loss; + = censored.

Table 4. Patient and graft losses in tacrolimus- and cyclosporin microemulsion (ME)-treated patients at 3 years after simultaneous pancreas–kidney transplantation

	Tacrolimus ($n=103$)	Cyclosporin-ME ($n=102$)
Death	5	3
Cardiovascular	2	1
Infection	1	2
Brain oedema	1	0
Suicide	1	0
Pancreas graft losses	11	28
Rejection	4	8
Thrombosis	2	10[a]
Infection	1	3
Haemorrhage	1	3
Non-viable graft	1	0
Leakage	0	1
Fibrotic pancreas	0	1
Insulin resistance	1	1
Splenic artery stenosis	1	0
Decreased function	0	1
Death with a functioning graft	2	2
Kidney graft losses	6	8
Rejection	3	2
Pseudoaneurysm	1	0
Thrombosis	0	1
Procedural complications	0	2
Acute tubular necrosis	1	1
Infection	1	2
Death with a functioning graft	2	2

[a] $P=0.0185$ *vs* tacrolimus.

Mean fasting glucose was 88 ± 12 mg/dl in the tacrolimus group and 86 ± 17 mg/dl in the cyclosporin-ME group. Corresponding mean levels of fasting C-peptide were also similar (2.49 ± 1.30 and 2.89 ± 1.32 ng/ml, respectively). However, HbA_{1C} was significantly higher in the tacrolimus group ($5.2\pm0.7\%$) than in the cyclosporin-ME group ($5.0\pm0.6\%$; $P=0.02$). None of the patients in either group had HbA_{1C} $\geq7\%$, although six out of 53 patients in the tacrolimus group and one out of 35 in the cyclosporin-ME group had an HbA_{1C} value $\geq6\%$.

Renal graft function in the patients remaining in the study at 3 years (as assessed by measuring serum creatinine concentrations) was almost identical in patients treated with tacrolimus- (1.4 ± 0.5 mg/dl) and cyclosporin-ME-based therapy (1.4 ± 0.3 mg/dl). Creatinine clearance was also comparable in the two treatment groups (67 ± 25 *vs* 66 ± 16 ml/min).

Cardiovascular risk factors

Throughout the study, total cholesterol and triglyceride values tended to be lower in the tacrolimus group than in the cyclosporin-ME group. At 3 years post-transplant, total cholesterol was 169 ± 36 mg/dl in the tacrolimus group ($n=56$) and 194 ± 39 mg/dl ($n=40$) in the cyclosporin-ME group ($P=0.001$). The corresponding values for triglycerides were 87 ± 51 mg/dl ($n=54$) and 101 ± 41 mg/dl ($n=39$), respectively ($P=0.04$). No differences were detected in high-density lipoprotein or low-density lipoprotein cholesterol, and there were no differences between the two groups regarding the number of patients receiving lipid-lowering drugs (15% tacrolimus and 17% cyclosporin-ME).

Arterial blood pressure was comparable in the two treatment groups throughout the study. At the end of 3 years, the mean blood pressure was $130/77\pm20/13$ mmHg ($n=48$) in the tacrolimus group and $132/76\pm17/11$ mmHg ($n=38$) in the cyclosporin-ME group. Likewise, there was no difference in the number of patients receiving antihypertensive treatment (35 *vs* 51%, respectively) or in the mean number of antihypertensive medications used (1.89 *vs* 1.62).

Sixteen (15.5%) patients receiving tacrolimus and 15 (14.7%) receiving cyclosporin-ME developed peripheral vascular disease during the study (five out of 16 tacrolimus- and four out of 15 cyclosporin-ME-treated patients had pre-existing peripheral vascular disease). This resulted in foot or toe ulcers in 16 patients (tacrolimus $n=7$, cyclosporin-ME $n=9$); toe amputation in nine patients (tacrolimus $n=7$, cyclosporin-ME $n=2$); lower leg amputation in two patients ($n=1$ in each treatment group); and an angioplasty in four patients (tacrolimus $n=1$, cyclosporin-ME $n=3$).

The occurrence of cardiac or cerebral complications was recorded over the 3 years, even if patients were withdrawn from the study. In the tacrolimus group, seven patients suffered from a cardiovascular event and four from a cerebrovascular event; two of them died from heart failure. In the cyclosporin-ME group, six patients suffered from cardiovascular events, one event of which was fatal. The differences between the two groups were not significant.

Infection, malignancy and hospitalization

The overall frequency of urinary tract infection, CMV infection, peritonitis and polyomavirus nephropathy during the 3 years post-transplant was similar in the two treatment groups (Table 5). A single case of cancer (native kidney carcinoma) was reported in the tacrolimus group and three cases (colon, squamous cell carcinoma and uterine carcinoma) were reported in the cyclosporin-ME group.

During the first post-transplant year, there were 242 hospitalizations among the 102 patients in the tacrolimus group (2.37 hospitalizations/patient) and 211 hospital admissions among 101 patients in the cyclosporin-ME group (2.09 hospitalizations/patient). Forty-one (40%) patients in the tacrolimus group and 46 (46%) in the cyclosporin-ME group had only one hospital admission during this first year. There was a significant difference in favour of tacrolimus compared with cyclosporin-ME with respect to duration of hospitalization (tacrolimus, mean duration, 20 ± 19 days; total duration, 4769 days; cyclosporin-ME, 26 ± 25 and 5354 days, respectively; $P=0.009$). A similar analysis over the entire 3-year study indicated that there were 345 hospitalizations in the tacrolimus group and 289 hospital admissions in the

Table 5. Cumulative occurrence of infections, rehospitalizations and surgical cases during the 3 years after simultaneous pancreas–kidney transplantation

	Tacrolimus ($n=103$)	Cyclosporin-ME ($n=102$)
Primary infection [*n* (%)]		
Urinary tract infection	43 (42)	45 (44)
Cytomegalovirus (CMV)	35 (34)	35 (34)
CMV infection	32	32
CMV disease	3	3
Peritonitis	11 (11)	18 (18)
Polyomavirus	2 (2)	0
Rehospitalization[a] [*n* (%)]	$n=243$	$n=188$
Infection	72 (30)	54 (29)
Routine	48 (20)	31 (16)
Rejection	40 (16)	36 (19)
Surgery	18 (7)	20 (11)
Cardiovascular	19 (8)	17 (9)
Gastrointestinal	15 (6)	12 (6)
Eyes	6 (2)	2 (1)
Other	21 (9)	16 (9)
Unknown reasons	4 (2)	0
Cases of surgery (*n*)		
<24 h	7	19
Other cases	38	55

[a]Excluding hospital stay for transplantation.

cyclosporin-ME group. At this time, there was no significant difference between treatment groups for duration of hospitalization (tacrolimus, mean duration, 16 ± 18 days; total duration, 5667 days; cyclosporin-ME, 21 ± 23 days and 5914 days, respectively). No differences were detected between the groups regarding the reasons for rehospitalization (Table 5).

Tacrolimus treatment was associated with a significantly lower incidence of surgical events (0.186 events/100 patients/year) than cyclosporin-ME therapy (0.489 events/100 patients/year; $P=0.01$).

Discussion

SPK transplantation currently represents the best treatment option for most type 1 diabetic patients with end-stage kidney disease and has been shown to provide a better prognosis than isolated kidney transplantation [4,5]. According to the International Pancreas Transplant Registry [15], 3-year survival rates improved between 1988–1991 and 1998–1999 from 83 to 91% for patient survival and from 70 to 78% for pancreas survival. This was attributed primarily to a reduction in technical failure rate. The report showed that pancreas graft thrombosis accounted for >70% of technical graft losses irrespective of duct management technique [15]. The second most important cause of pancreas graft loss was rejection, accounting for a 2–6% decrease in graft survival during the first year post-transplant. It is also likely that a considerable number of graft thromboses are triggered by rejection [16].

Although safe and effective immunosuppressive therapy has opened the way for future progress, most regimens are supported only by single-centre or registry reports; controlled, multicentre, prospective, randomized studies evaluating the use of newer immunosuppressive drugs in pancreas transplantation are lacking. The Euro-SPK Study Group was established to exploit the joint co-operative potential of different European and Israeli transplant centres. The first common project, Euro-SPK 001, compared the effect of tacrolimus- and cyclosporin-ME-based immunosuppressive regimens in SPK transplantation and was designed to serve as a reference trial in this field.

Previously published results of the 1-year findings from this study demonstrated a better outcome in tacrolimus- compared with cyclosporin-ME-treated patients in terms of improved pancreas graft survival and lower rates of moderate or severe rejection [12]. The main difference between treatment groups, accounting for almost a 17% lower 1-year pancreas graft survival rate in the cyclosporin-ME group (74.5 *vs* 91.3% for tacrolimus; $P=0.001$), was the higher incidence of graft thrombosis among patients treated with cyclosporin-ME. The 1-year results also showed that more patients treated with cyclosporin-ME than with tacrolimus (53 *vs* 23%; $P<0.0001$) were withdrawn from the study, with graft loss and a switch to alternative immunosuppressive therapy the most common reasons for withdrawal. In addition, significantly fewer patients treated with tacrolimus than with cyclosporin-ME required a switch in immunosuppressive therapy (5.8 *vs* 33.3%; $P<0.0001$). During the first year, there was only one case of kidney or pancreas graft rejection rated as moderate or severe according to Banff classification (or grade III and IV according to Drachenberg *et al.*) in the tacrolimus group compared with 12 such cases in the cyclosporin-ME group ($P=0.005$) [12].

At 3 years post-transplant, fewer patients receiving tacrolimus than those receiving cyclosporin-ME were excluded from the study ($P=0.003$). In the cyclosporin-ME group, exclusion was mainly due to graft loss and switch to tacrolimus, while MMF withdrawal was the most common reason in the tacrolimus group. The latter finding also confirms the results of previous studies showing that tacrolimus-treated patients require significantly lower doses of MMF than those administered cyclosporin-ME [17]. The interaction between MMF and tacrolimus is attributable to an inhibitory effect of tacrolimus on mycophenolic acid glucuronidation [18] and should be corrected by appropriate dosage adjustment performed in advance.

As observed at 1 year, there were no differences between the tacrolimus and cyclosporin-ME arms in patient survival and kidney graft survival. The significant difference in pancreas survival in favour of tacrolimus seen at 1 year was also maintained at 3 years ($P=0.002$; Figure 2), with only two additional losses in each group.

Almost all clinical or biopsy-proven rejection episodes occurred during the first year of follow-up, and rejection-free survival at 3 years was not statistically different between the study groups (Figure 1). Of note, however, there was only a single case of moderate or severe rejection in the tacrolimus group compared with 17 such cases in the cyclosporin-ME group. Despite the reduced severity of rejection associated with tacrolimus *vs* cyclosporin-ME therapy, graft loss by 3 years was more frequent among tacrolimus-treated patients with previous rejection episodes than among those who were free of rejection ($P = 0.01$), while in the cyclosporin-ME group graft loss occurred at a roughly equal frequency in those with and without previous rejection. This finding suggests that the reduced efficacy observed with cyclosporin-ME in pancreas transplantation may be due to an involvement of non-immunological factors. Indeed, one of the most notable differences between the treatment groups in this study was the higher rate of pancreas graft thrombosis among patients receiving cyclosporin-ME (10 *vs* two cases with tacrolimus; $P = 0.02$). All these findings support a hypothesis that the use of tacrolimus, in addition to having a superior immunological effect, confers a specific advantage in pancreas transplantation.

More frequent thrombotic complications and enhanced *in vitro* pro-coagulation activity in patients treated with cyclosporin have been reported previously [19,20], including pancreas transplant recipients [21]. However, this was not confirmed in subsequent studies [22–25]. A recently published prospective, randomized, multicentre study comparing the use of tacrolimus- and cyclosporin-ME-based therapy in combination with azathioprine in 557 kidney recipients found no between-group differences in the rate of renal graft thrombosis [26]. Furthermore, other forms of thromboses, mainly occlusions of the vascular dialysis access, were more frequent with tacrolimus than with cyclosporin-ME [26]. Pancreas graft thrombosis may occur due to a number of reasons [27], including donor and recipient factors, technical error, rejection, microcirculation abnormalities and the type of immunosuppressive therapy. A beneficial effect of tacrolimus over cyclosporin in preventing pancreas graft thrombosis has been suggested by Kandaswamy *et al*. [28]; our data represent the first confirmation of this finding in a large randomized, controlled study.

In conclusion, the superiority of a tacrolimus- over a cyclosporin-ME-based immunosuppressive regimen was demonstrated by the 3-year results of this Euro-SPK 001 trial. The use of tacrolimus resulted in improved long-term pancreas graft survival, a lower rate of moderate or severe rejection and fewer pancreas graft thromboses. Patient and kidney survival as well as adverse event occurrence were comparable between the two treatment groups. The results of this first European multicentre study provide a basis of reference for future clinical trials in pancreas transplantation.

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