A large, prospective, randomized, open-label, multicentre study of corticosteroid withdrawal in SPK transplantation: a 3-year report

Richard Nakache¹, Jacques Malaise², Dominique Van Ophem² and the Euro-SPK Study Group

¹Transplantation Unit, Department of Surgery B, Tel Aviv Sourasky Medical Center, Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel and ²Department of Kidney and Pancreas Transplantation and Organ Procurement, Cliniques Universitaires St Luc, Université Catholique de Louvain, Brussels, Belgium

Abstract

Background. Simultaneous pancreas–kidney (SPK) transplantation is the treatment of choice for selected diabetic patients. Corticosteroids are an important element of immunosuppressive protocols, but their long-term use has detrimental effects on patients’ health, necessitating eventual discontinuation.

Methods. This prospective study evaluated the safety and feasibility of corticosteroid withdrawal in 205 SPK transplant recipients randomized to immunosuppressive treatment with either tacrolimus and mycophenolate mofetil (MMF) (n = 103) or cyclosporin microemulsion (ME) and MMF (n = 102).

Results. Corticosteroid withdrawal was successful in the majority of in-study patients (66% tacrolimus, 73% cyclosporin-ME). Compared with out-of-study patients or those continuing corticosteroid therapy, in-study patients withdrawn from corticosteroids experienced fewer pancreas or kidney graft losses, fewer episodes of acute rejection and were less likely to be withdrawn from the study. Acute rejection occurred after corticosteroid withdrawal in two patients who had a previous rejection and in five patients who were rejection-free before corticosteroid withdrawal. No rejection episodes were associated with graft loss or immediate serious consequences. Overall, corticosteroid withdrawal was achieved with an increase in the dose of both MMF and tacrolimus.

Conclusions. A long-term survey of corticosteroid withdrawal in SPK transplantation with multifactorial analyses is necessary to confirm these early results and to evaluate the positive effects on glucose metabolism and hypertension.

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

Introduction

Despite continuous progress in islet cell transplantation, whole-pancreas transplantation is the treatment of choice for selected diabetic patients. As a result of advances in surgical technique and the introduction of newer immunosuppressive regimens, such as tacrolimus and mycophenolate mofetil (MMF), there has been a substantial improvement in short-term outcomes, with 1-year pancreas graft survival rates in excess of 80%. Current procedures are also associated with a detectable enhancement in long-term graft survival, both in pancreas and in simultaneous pancreas–kidney (SPK) transplantation [1].

Corticosteroids, traditionally used in induction immunosuppression, serve as the mainstay for maintenance therapy in organ transplant recipients. Despite their essential role in the prevention of graft rejection, long-term corticosteroid use is associated with serious adverse events (e.g. osteoporosis, bone fractures, avascular necrosis, post-transplant diabetes mellitus, arterial hypertension and cataracts), which in turn are associated with increased health care expenditure [2,3]. As such, corticosteroid withdrawal is an important objective of modern immunosuppressive therapy.

Here, we present an evaluation of the safety and feasibility of corticosteroid withdrawal based on the findings of the Euro-SPK 001 study [4], which compared maintenance immunosuppressive therapy with tacrolimus and MMF vs cyclosporin microemulsion (cyclosporin-ME) and MMF in SPK recipients. This study is the largest prospective, randomized trial of corticosteroid withdrawal in the SPK transplantation setting.
Steroid withdrawal in SPK transplantation

Patients and methods

The study methods and patient population have been described in full previously [4] and also elsewhere in this supplement (Saudek et al.). Details of the immunosuppression regimen are given below.

Immunosuppressive therapy

In total, 205 C-peptide-negative patients with type 1 insulin-dependent diabetes mellitus undergoing SPK transplantation were randomized pre-operatively to receive either tacrolimus (103 patients) or cyclosporin-ME (102 patients). All patients received quadruple immunosuppressive induction therapy, which comprised anti-thymocyte antibodies, methylprednisolone, MMF and tacrolimus or cyclosporin-ME. Thereafter, patients received maintenance therapy with tacrolimus or cyclosporin-ME, MMF and prednisone.

The recommended initial oral daily dose of tacrolimus was 0.2 mg/kg, with subsequent doses titrated to give whole-blood trough levels of 8–15 ng/ml by day 5. The initial oral dose of cyclosporin-ME was 7 mg/kg/day, with subsequent dosing titrated to achieve whole-blood trough levels between 150 and 250 mg/ml by day 5. Both groups of patients received 2 g of MMF prior to transplantation. The first post-operative dose of MMF was administered preferably within 24 h of skin closure but imperatively within 72 h. The recommended daily dose of MMF was 1 g b.i.d., adjusted according to side effects. Anti-thymocyte globulin (ATG-Fresenius 4 mg/kg/day or Thymoglobulin® 1.25 mg/kg/day) was initiated perioperatively, before clamp release, followed by three daily post-operative doses.

Corticosteroid withdrawal protocol

All patients received intravenous methylprednisolone: 500 mg on day 0 and 125 mg on day 1. This was followed by oral prednisone, administered at 20 mg on days 2–14, 15 mg on days 15–28, 10 mg on days 29–42 and 5 mg on days 43–90. Thereafter, corticosteroid therapy was stopped altogether. The recommended doses were adjusted according to body weight. In all cases, the slow corticosteroid taper was started by month 3 post-transplant at the latest, with complete withdrawal being achieved within a further 3-month interval.

Two subgroups of patients were defined at 3 years post-transplantation: those who were receiving corticosteroid-free immunosuppression and those continuing to receive corticosteroids, even if corticosteroids had been temporarily stopped.

Diagnosis of rejection

If pancreas or kidney graft rejection was suspected, biopsy samples were taken and analysed by a local histopathologist. Renal biopsies were graded as borderline, mild, moderate or severe in accordance with the Banff classification [5]. Pancreas biopsies were graded according to the Drachenberg scale [6].

Other assessments

Kidney and pancreas graft function, blood pressure, as well as lipid and haematology data were assessed for those patients who remained in the study at 3 years.

Statistical analysis

$\chi^2$ and Fisher’s exact tests were used to compare categorical variables. The Mann–Whitney U-test was used to compare continuous variables. Survival rates and time-dependent variable rates were obtained using the Kaplan–Meier method and compared using the log-rank test. Values of $P < 0.05$ were considered to be statistically significant. Mean values are expressed with SDs.

Results

Corticosteroid withdrawal

In the majority of patients in both treatment groups, corticosteroid withdrawal was achieved between 6 months and 1 year post-transplantation. As shown in Figure 1, there was no significant difference between the tacrolimus group and the cyclosporin-ME group in terms of the proportion of patients who remained on corticosteroid therapy during the study; at 3 years post-transplant, 34.1% of tacrolimus- and 26.8% of cyclosporin-ME-treated patients were receiving corticosteroid treatment. The mean time to achieve corticosteroid withdrawal was longer in the tacrolimus group (279 days) than in the cyclosporin-ME group (236 days; $P = 0.04$).

Corticosteroid withdrawal in patients remaining on study treatment

In total, 75 patients in the tacrolimus group and 47 patients randomized to cyclosporin-ME-based treatment remained in the study. Over the 3-year follow-up, corticosteroid withdrawal was achieved in 54 in-study patients receiving tacrolimus (day 93–621) and in 37 such patients receiving cyclosporin-ME (day 100–916).

In the tacrolimus group, corticosteroids were withdrawn in 39 patients during the first year, 15 patients during the second year and none during the third year. Ten of the 54 patients were withdrawn from the study, even if corticosteroids had been temporarily stopped.

Fig. 1. Actuarial analysis of patients continuing treatment with corticosteroids following SPK transplantation (Kaplan–Meier). O = corticosteroid stop; + = censored.
six of whom remained corticosteroid-free at 3 years. In one of the six patients, sirolimus therapy was added to the tacrolimus regimen for chronic rejection before the end of the first year; this patient remained corticosteroid-free until he received a second kidney transplant during the third year. One patient who developed diabetes during the second year post-transplant was switched to cyclosporin-ME and then to sirolimus without corticosteroids; this patient subsequently suffered pancreas graft loss due to chronic rejection during the third year. Two other patients were receiving tacrolimus monotherapy at 3 years. Another patient was withdrawn from MMF because of cancer and was receiving tacrolimus and sirolimus. The remaining patient was switched to cyclosporin-ME for epilepsy and remained corticosteroid-free at 3 years. In the other four patients withdrawn from the study, corticosteroids were temporarily re-administered in two following MMF dose reduction (in both cases, insulin was restarted for poor pancreas function). Long-term corticosteroids were restarted in another patient who experienced rejection following tacrolimus withdrawal because of polyomavirus nephropathy. The current corticosteroid status is unknown for the remaining patient who suffered end-stage renal disease from chronic rejection and received a kidney retransplant during the third year.

Corticosteroids were also re-administered to one patient following a substantial decrease in MMF dose. This patient remained on study medication at 3 years.

In the cyclosporin-ME group, corticosteroids were withdrawn in 34 patients during the first year post-transplant, in two patients during the second year and in one patient during the third year. Four of the 37 patients subsequently were withdrawn from the study: three were switched to tacrolimus (one each for rejection, hirsutism and gingival hyperplasia) and remained corticosteroid-free at 3 years; another patient who was corticosteroid-free at 2 years was lost to follow-up. Corticosteroids were restarted during the first year post-transplant in one patient as a result of MMF dose reduction. This patient remained in the study at 3 years.

Among the patients remaining in the study at 3 years, corticosteroids were never withdrawn in 21 patients in the tacrolimus treatment group and in 10 patients in the cyclosporin-ME group.

Corticosteroid withdrawal in patients withdrawn from the study

In total, 28 patients in the tacrolimus group and 55 patients in the cyclosporin-ME group were withdrawn from the study. Corticosteroids were withdrawn successfully in four out-of-study patients in the tacrolimus group and in 10 such patients from the cyclosporin-ME group. The reasons for study cessation among the patients withdrawn from corticosteroids in the tacrolimus group were two early pancreatic thromboses, conversion from MMF to azathioprine, and switch to cyclosporin-ME for glucose intolerance. In the cyclosporin-ME group, there were two early pancreas losses due to infection, one early pancreas loss due to thrombosis and one due to rejection. In addition, there were four switches to tacrolimus treatment for rejection, one due to poor cyclosporin-ME absorption and one due to the development of hirsutism.

The remaining out-of-study patients (tacrolimus $n=24$, cyclosporin-ME $n=45$) had not been withdrawn from corticosteroids at any time during the 3-year study. The reasons for study withdrawal in these patients were: kidney loss, pancreas loss and death (tacrolimus $n=7$, cyclosporin-ME $n=18$); switch to alternative immunosuppressive drug (tacrolimus $n=4$, cyclosporin-ME $n=24$) and MMF withdrawal (tacrolimus $n=12$, cyclosporin-ME $n=2$). In addition, one patient in the tacrolimus group was lost to follow-up and one patient was withdrawn from cyclosporin-ME due to sepsis.

Post-transplant events

During the first 6 months post-transplantation, there were fewer pancreas and kidney graft losses, significantly fewer acute rejection episodes ($P=0.00001$) and fewer cases of study withdrawal among the in-study patients withdrawn from corticosteroids than among out-of-study patients or those continuing to receive corticosteroid therapy (Table 1). Likewise, between 6 months and 3 years post-transplant, there were fewer pancreas graft losses among in-study patients withdrawn from corticosteroids; also, significantly fewer patients in this subgroup were withdrawn from the study ($P=0.007$ vs out-of-study patients or those patients continuing to receive corticosteroids).

Acute rejection

The majority (62 out of 91; 68%) of in-study patients withdrawn from corticosteroids remained free from acute rejection during the 3-year observation period (72% tacrolimus, 62% cyclosporin-ME; Table 2). Among the 29 patients in this subgroup who developed acute rejection (tacrolimus $n=15$, cyclosporin-ME $n=14$), 22 experienced rejection before corticosteroid withdrawal (tacrolimus $n=12$, cyclosporin-ME $n=10$). Acute rejection occurred after corticosteroid withdrawal in two patients ($n=1$ in each treatment group) who had a previous rejection and in five patients (tacrolimus $n=2$, cyclosporin-ME $n=3$) who were rejection-free prior to corticosteroid withdrawal.

The three cases of acute rejection occurring after corticosteroid withdrawal in the tacrolimus group included an episode of mild (grade 1) antibody-sensitive rejection at 21 days after corticosteroid withdrawal and an episode of borderline corticosteroid-sensitive acute rejection occurring at 400 days after corticosteroid withdrawal. In both cases, corticosteroids were restarted. Corticosteroids were not reintroduced in the third patient who had corticosteroid-sensitive rejection 194 days after corticosteroid withdrawal.
In the cyclosporin-ME group, rejection episodes occurred 36, 79, 180 and 711 days after corticosteroid withdrawal and were grade 1 corticosteroid sensitive for two patients, grade 2 antibody resistant with conversion to tacrolimus in one case and grade 2 corticosteroid sensitive for the other patient. None of the patients had maintenance corticosteroid therapy reintroduced.

Late acute rejection, occurring >6 months post-transplantation, developed in patients who remained on corticosteroid therapy (in-study n = 1, out-of-study n = 8; Table 2). An additional 14 out-of-study patients (tacrolimus n = 4, cyclosporin-ME n = 10) stopped corticosteroid therapy, with no evidence of further acute rejection, as well as one tacrolimus-treated patient lost to follow-up at 3 years.

Overall, significantly fewer out-of-study patients continuing corticosteroid therapy remained free from rejection (29%) than was the case among in-study patients, irrespective of whether they completed corticosteroid withdrawal (68%; P = 0.00001) or not (52%; P < 0.05). The occurrence of more than one episode of rejection was also higher in out-of-study patients receiving maintenance corticosteroid therapy than in the other two subgroups (Table 2).

Graft function and lipids
As shown in Table 3, kidney function, as assessed by measurements of serum creatinine and creatinine clearance, was comparable in the corticosteroid withdrawal and corticosteroid maintenance groups. There was also no difference in kidney function between the tacrolimus and cyclosporin-ME groups. In terms of pancreas function, fasting C-peptide was lower in patients withdrawn from corticosteroids (2.6 ng/ml) than in those maintained on corticosteroids (4.4 ng/ml; P = 0.03) in the cyclosporin-ME group, whereas no significant difference was found in the tacrolimus group. Furthermore, in patients receiving

---

**Table 1. Post-transplant events**

<table>
<thead>
<tr>
<th></th>
<th>In-study patients withdrawn from CS</th>
<th>Other patients*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Tac</td>
<td>Cyc-ME</td>
</tr>
<tr>
<td>CS withdrawal</td>
<td>15/54</td>
<td>17/37</td>
</tr>
<tr>
<td>Acute rejection</td>
<td>13/54</td>
<td>11/37</td>
</tr>
<tr>
<td>Death</td>
<td>0/54</td>
<td>0/37</td>
</tr>
<tr>
<td>Pancreas loss</td>
<td>0/54</td>
<td>0/37</td>
</tr>
<tr>
<td>Kidney loss</td>
<td>0/54</td>
<td>0/37</td>
</tr>
<tr>
<td>Study withdrawal</td>
<td>0/54</td>
<td>0/37</td>
</tr>
</tbody>
</table>

*Tac = tacrolimus; Cyc-ME = cyclosporin microemulsion; CS = corticosteroids.

---

**Table 2. Acute rejection**

<table>
<thead>
<tr>
<th></th>
<th>In-study patients</th>
<th>Out-of-study patients</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>CS withdrawal</td>
<td>CS maintenance</td>
</tr>
<tr>
<td></td>
<td>Tac</td>
<td>Cyc-ME</td>
</tr>
<tr>
<td>Never rejected</td>
<td>39/54 (72)</td>
<td>23/37 (62)</td>
</tr>
<tr>
<td>Acute rejection</td>
<td>15/54</td>
<td>14/37</td>
</tr>
<tr>
<td>1 episode/patient</td>
<td>12</td>
<td>12</td>
</tr>
<tr>
<td>&gt;1 episodes/patient</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>After CS withdrawal</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>&gt;6 months post-Tx</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Tac = tacrolimus; Cyc-ME = cyclosporin microemulsion; CS = corticosteroid; Tx = transplantation.

*P = 0.00001; bP < 0.05; cP = 0.0001 vs corticosteroid maintenance in out-of-study patients.
maintenance corticosteroid therapy, C-peptide levels were significantly lower, while glycosylated haemoglobin was higher in patients assigned to tacrolimus treatment than to cyclosporin-ME treatment (Table 3).

At 3 years post-transplant, total cholesterol levels were significantly lower in patients treated with tacrolimus than with cyclosporin-ME, irrespective of corticosteroid use (Table 3).

**Immunosuppression**

At 3 years, in-study patients continuing to receive corticosteroids received lower daily doses of MMF than patients not receiving corticosteroids (1.2 vs 1.5 g/day, \( P < 0.05 \); Table 4). In addition, fewer patients maintained on corticosteroids (11%) received the recommended dose of 2 g/day MMF compared with those withdrawn from corticosteroids (41%; \( P = 0.0065 \)).

The mean daily dose of tacrolimus was significantly higher at 3 years among patients withdrawn from corticosteroids (0.09 mg/kg) than among those continuing corticosteroids (0.06 mg/kg; \( P < 0.05 \)), but both corticosteroid groups were comparable with respect to the mean daily dose of cyclosporin-ME and also the trough serum levels of tacrolimus and cyclosporin-ME (Table 4).

In-study patients maintained on corticosteroids and treated with tacrolimus received a lower mean total daily dose of prednisone compared with cyclosporin-ME-treated patients in this subgroup (6 vs 11 mg, respectively; \( P = 0.009 \)). Similarly, the mean dose of corticosteroids was 3 mg/day in the tacrolimus group and 11 mg/day in the cyclosporin-ME group (\( P = 0.02 \)). Overall, corticosteroid withdrawal was achieved with an increase in MMF dose for both tacrolimus and cyclosporin-ME treatment groups and with an increase in the tacrolimus dose.
Discussion

Recent improvements in patient and graft survival and control of allograft rejection have enabled SPK transplantation to achieve the same level of safety as that attained in renal transplantation. In both fields, emphasis has been placed on improving long-term graft function and quality of life. The continuing advances in immunosuppressive therapy have enabled physicians to modulate the numerous risk factors linked with deterioration of graft function and morbidity. In the current era of immunosuppression minimization, trends are focused towards achieving corticosteroid-sparing protocols. In fact, a recently conducted study indicated that given a risk-free choice, patients generally preferred withdrawal of corticosteroids over withdrawal of any other agent, including calcineurin inhibitors [7].

Two routine approaches for limiting corticosteroid-related side effects are systematic corticosteroid withdrawal in stable allograft recipients and complete corticosteroid avoidance or rapid corticosteroid elimination in recipients with undetermined graft function. Clinicians have been reluctant to attempt complete corticosteroid avoidance in renal transplantation for fear of exposing patients to acute rejection or intense lymphocyte-depleting induction therapy. However, centres that have employed the avoidance or rapid elimination approach report excellent patient and graft survival, as well as low rates of acute rejection (0–10%) in small series of low-risk kidney recipients [8–12]. In contrast, other centres have found that rates of rejection are higher in recipients undergoing rapid corticosteroid discontinuation than in those maintained on corticosteroid therapy, though there was no impact on renal function [13,14]. Interestingly, protocol biopsies obtained from the corticosteroid withdrawal group revealed higher levels of transforming growth factor-β and greater fibrosis. These results have not been confirmed by larger studies [15].

Corticosteroid withdrawal would normally be undertaken in situations where there is: (i) good long-term graft prognosis; (ii) evidence of corticosteroid-induced morbidity; or (iii) at a patient’s request. However, the absence of a strong clinical marker for successful corticosteroid withdrawal means that the decision to withdraw corticosteroids from stable renal or pancreas recipients is far from easy. Earlier protocols involving delayed corticosteroid withdrawal in stable renal transplant recipients met with mixed success [16] and initial cyclosporin-ME-based trials showed an ~30% likelihood of acute and/or chronic rejection with late corticosteroid withdrawal [17]. Based on these results, virtually all renal transplant patients presently are maintained indefinitely on low-dose corticosteroids. However, other prospective trials supported the view that in 80% of patients receiving cyclosporin-ME-based triple therapy, late corticosteroid withdrawal poses little short-term risk to the renal graft; however, because of the possibility of an insidious increase in plasma creatinine levels, there is a need to monitor long-term graft function [18]. It has also been shown that the addition of MMF to cyclosporin-ME enables prednisone withdrawal at 6 months post-transplant without an increase in acute rejection [19]. Likewise, sirolimus was added to cyclosporin-ME maintenance therapy, corticosteroid tapering (initiated at a mean of 415 days post-transplant) was maintained for 3 years in 78% of kidney recipients [20].

Tacrolimus-based immunosuppression also enables successful corticosteroid withdrawal [21], and better results have been reported for tacrolimus in combination with MMF than for tacrolimus combined with azathioprine [22]. A study employing tacrolimus and MMF maintenance immunosuppression reported a 94% likelihood of patients being maintained off corticosteroids following late corticosteroid withdrawal, with excellent graft function and a low incidence of post-transplant diabetes mellitus at 2 years [23]. In addition, an analysis of >800 tacrolimus-treated renal transplant recipients randomized to withdrawal of either MMF or corticosteroids at 3 months post-transplantation showed that the overall 6-month incidence of biopsy-proven acute rejection was similar for all treatment groups (15.1% corticosteroid stop; 14.8% MMF stop; and 17.0% tacrolimus-based triple therapy) [24].

The timing of corticosteroid withdrawal and the choice of maintenance immunosuppression are likely to be important factors for success. In a meta-analysis including 1461 patients, the issue of late corticosteroid withdrawal has been assessed by the European Best Practice Guidelines Group [25]. The findings suggested that late corticosteroid withdrawal should be restricted to low-risk patients because of the potential for acute rejection. The survey also showed that significantly more patients in the prednisone withdrawal group than in the control group lost their kidney 1–3 years post-transplantation. Based on an estimated relative risk of 1.40 graft failures, it was recommended that corticosteroid withdrawal should be accompanied by extended graft monitoring and corticosteroid re-administration in the case of chronic allograft dysfunction.

Few studies have investigated the long-term effects of corticosteroid avoidance or rapid elimination in transplant patients, and it remains unclear whether or not the limited use of corticosteroids has the potential to jeopardize graft survival. A 4-year analysis of 724 patients enrolled in the Collaborative Transplant Study showed that 90% of the grafts functioned without corticosteroids [26]. These patients had been receiving corticosteroids for a minimum of 6 months after transplantation and were clinically stable at the time of corticosteroid elimination. While the data predicted a 21.4-year graft half-life for these transplants, the analysis failed to account for the possible influence of corticosteroid withdrawal on chronic graft nephropathy.

Corticosteroid withdrawal is a desirable objective in pancreas transplant patients receiving calcineurin inhibitors, since there is an obvious correlation between corticosteroid exposure and complications such as
hypertension, hyperlipidaemia and glucose intolerance [27], with an associated decline in health-related fitness [28]. Based on the encouraging results obtained with corticosteroid withdrawal in renal transplantation, a number of transplant centres have begun to offer corticosteroid-free regimens to pancreas recipients either immediately at transplantation or as soon as a stable and well-functioning graft has been achieved. Many centres have published reports of successful conversion to a corticosteroid-free protocol, showing beneficial effects [29–32]. Very few clinicians who choose rapid elimination or avoidance of corticosteroids in pancreas transplantation have traded long-term corticosteroid exposure for intense antibody induction. Kaufman et al. conducted a small, prospective, randomized study of rapid elimination of corticosteroids in 40 SPK transplant patients receiving tacrolimus-based immunosuppression and intensified induction therapy [32]. Outcomes were excellent, with only one patient developing an episode of acute rejection and no cases of late rejection. In another study, ATG induction therapy for 10 days in combination with cyclosporin-ME and MMF without corticosteroids was administered to 28 SPK transplant recipients [33]. Although the incidence of rejection was low (7%), there was a high incidence of viral infection and post-transplant lymphoproliferative disease.

A large, retrospective study of slow withdrawal of corticosteroids in 141 pancreas transplant patients showed that tacrolimus-based immunosuppression without anti-lymphocyte induction was not associated with an increased risk of rejection [30,31]. In this study, 58 of 124 patients were able to eliminate corticosteroid use completely between 4 and 40 months after transplantation, with excellent outcome. These preliminary findings are supported by the results of a prospective study in 35 SPK transplant patients receiving the same maintenance immunosuppression protocol [34]. In this study, corticosteroid withdrawal was safely achieved at 3 years in 69% of patients. Furthermore, a retrospective, single-centre analysis of 46 SPK transplant patients undergoing corticosteroid withdrawal at 3 months post-transplant while receiving immunosuppression based on either one of the calcineurin inhibitors suggests that safer and earlier corticosteroid withdrawal and a better graft survival is possible with MMF as opposed to azathioprine as adjunctive therapy [35]. The tacrolimus–MMF drug combination was used as maintenance immunosuppression in a prospective study involving 55 rejection-free and insulin-free pancreas recipients randomized at 6 months after transplantation to standard triple therapy or corticosteroid withdrawal [36]. There were no differences between the two treatment groups in terms of rejection, graft function, and patient and graft survival at the 6-month follow-up.

Together, these results of corticosteroid withdrawal are substantiated by our own findings. In this prospective, randomized, multicentre study, the actuarial rate of corticosteroid withdrawal in SPK transplant patients was similar with tacrolimus treatment (66%) and cyclosporin-ME (73%). In-study patients withdrawn from corticosteroids experienced fewer pancreas or kidney graft losses, fewer episodes of acute rejection and fewer withdrawals from the study than did patients who were out-of-study or who continued corticosteroid therapy. Overall, more patients continuing in the study remained rejection-free, irrespective of corticosteroid use, than was the case among those discontinuing the study. This is mainly due to the use of precise selection criteria for corticosteroid withdrawal. In this context, there were only a few rejection episodes or other complications after corticosteroid withdrawal and, in cases where rejection occurred, there was no graft loss or other serious outcomes. The successful elimination of corticosteroids was achieved together with an increase in the dose of both MMF and tacrolimus.

In conclusion, corticosteroid withdrawal was successful in the majority of SPK transplant recipients. A long-term survey of corticosteroid withdrawal in SPK transplantation with multifactorial analysis will be necessary to confirm these early results and to evaluate the positive effects of corticosteroid withdrawal on glucose metabolism and hypertension.

Acknowledgements. The Euro-SPK Study Group; see Appendix 1. Funding source. See Appendix 2.

Conflict of interest statement. None declared.

References

1. Gruesner AC, Sutherland DE. Pancreas transplant outcomes for United States (US) cases reported to the United Network for Organ Sharing (UNOS) and non-US cases reported to the International Pancreas Transplant Registry (IPTR) as of October 2000. Clin Transplant 2000; 45–72
Steroid withdrawal in SPK transplantation


