The Review of DIABETIC STUDIES

REVIEW

Tailored Immunosuppression and Steroid Withdrawal in Pancreas-Kidney Transplantation

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Abstract

BACKGROUND: Recent improvements in simultaneous pancreas-kidney transplantation (SPK) and the striking decrease in acute rejection lead us to focus on the effects of long-term immunosuppression. AIM OF THIS STUDY: Evaluation of a policy of steroid withdrawal and tailored immunosuppression in pancreas-kidney patients treated in a single center. METHODS: review of the clinical charts in 9 SPK recipients (male/female = 5/4, median age 41 years, median follow-up 42 months), by the same operator, under supervision of the two usual caregivers. Therapeutic protocols. Induction phase: all patients received mycophenolate mophetil (starting dose: 2 grams), tacrolimus and steroids, 8 received Simulect, 1 received thymoglobulins. Maintenance therapy was slowly reduced, with the goal of steroid withdrawal. RESULTS: The therapeutic adjustments were mainly determined by two almost opposing elements: 1. Rapid adjustments in the case of side-effects (gastrointestinal problems, infections and neoplasia); 2. Slow tapering off in the case of good organ function. On the other hand, a switch to cyclosporine A and to rapamycine was considered in the case of chronic organ malfunction. By these means, over a median of 42 months follow-up, steroid withdrawal was slowly obtained in 6/9 patients (at a median time of 25 months). CONCLUSIONS: Within the limits of this small-scale study, a tailored immunosuppressive policy allows at least some "positively selected" patients to reach the "dream" of steroid withdrawal after SPK.

Keywords: pancreas-kidney transplantation · immunosuppression · diabetes mellitus · renal replacement therapy

Introduction

Simultaneous pancreas-kidney transplantation (SPK) has enjoyed increasing success over the last decade, and is currently considered almost universally to be the best therapy for type 1 diabetic patients with end-stage renal disease (ESRD) [1-3]. Improvements in the surgical techniques and advances in immunosuppression have considerably reduced some crucial short-term problems, such as acute rejection or primary non-function. Consequently, interest is now shifting towards long-term problems and increasingly focuses on the management of chronic immunosuppression [4-6]. As median organ survival increased up to two decades, the long-term detrimental effects of immunosuppressive drugs on the cardiovascular system, and the risk of infectious diseases and neoplasia, are the new obstacles to be overcome, in order to improve the quality and quantity of life of our patients [1-6].

Furthermore, as a result of the improvements in surgical and medical therapies in this field, the indications for kidney-pancreas transplantation proliferate. Patients in earlier stages of kidney disease, as well as older patients and patients with high comorbidity can be considered for this therapy. However, this policy presents two almost opposing problems. The pre-emptive indications shift the balance between costs and benefits: in fact, the advantages of transplantation are readily appreciated in end-stage renal disease, con-

 DOI 10.1900/RDS.2004.1.3.129

sidering the grim prognosis of diabetic patients on dialysis. Failure or morbidity are considered with even higher concern in the case of "early" pre-emptive grafts, performed when the diabetic complications are present but not yet severe [7]. Conversely, the selection for transplantation of older and more complex patients, with increased comorbidity, mainly of cardiovascular origin, adds to the recipient pool of fragile patients. These patients are more prone to develop short-term complications, as well as long-term adverse effects of immunosuppression. Of particular importance in this regard is the impact on the cardiovascular system, taking into account the baseline problems frequently encountered in this population, and the increased risk of vasculopathy in patients treated with corticosteroids, or of hypertension in patients treated with calcineurine inhibitors [3, 6].

The "ideal immunosuppressive protocol" is a matter of debate. Over time, immunosuppressant schemes have followed the common trend of a first induction phase at high doses and with several drugs, followed by a second phase with lower-to-minimal doses, the "post-adaptation" therapy. The pre-adaptation phase is more easily standardized, a feature that is shared by several acute, short-term approaches in medicine. A tailored approach is more favorable for the second, long-term phase and should be based upon patients' characteristics [6]. The therapy should also account for the potential side-effects (infection, leukopenia in the first months; hypertension, cataract, muscular wasting, to cite some of the most common, in the further follow-up), and be modulated as the case may be.

In the setting of "minimal" short-term immunosuppression, steroid withdrawal is considered to be one of the most important therapeutic goals [8]. While indications and protocols are well defined in the field of kidney transplantation, knowledge is limited on SPK, also because of the smoldering nature of isolated pancreas rejection, in contrast with the relatively easier diagnosis in cases where the kidney is involved [4, 9, 10]. In this context, the present study reports on medium-term data, including the induction and the post-adaption phase, with tailored immunosuppression therapy in a small cohort of patients who received a pancreas-kidney graft in the Transplant Center of the University of Turin, Italy. The critical analysis of this relatively unexplored area has the further potential of provoking discussion on the crucial topic of long-term immunosuppression in fragile patients.

Patients and methods (setting of study)

The Chair of Nephrology at the University of Turin, Italy, has been running an active kidney transplant program since 1981 (1,747 grafts performed at August 31, 2004). From the early beginning, a low-steroid policy was followed, with tailored immunosuppressant schemas. In this same setting, 9 consecutive pancreas-kidney transplants were performed between August 1999 and July 2002 (M/F = 5/4; median age at graft: 41 years; median follow-up after graft at August 2004: 42 months).

The technique of portal-venous anastomosis and of enteric drainage was used in all cases. The patients were followed in the same setting as kidney transplant patients, by the same nephrological team, employing diabetologists or other specialists as consultants. Biochemical controls were planned thrice weekly in the first months after hospitalization; up to once every 2-3 weeks in the case of good organ function, one year after graft. Clinical controls were tailored to the clinical situation, and the control protocol was individualized one year after graft.

Parameters analyzed

Clinical and follow-up data were gathered from the clinical charts of the Kidney Transplant Center of Turin. The usual biochemical parameters employed in the clinical follow-up of transplant patients were analyzed in the same setting (laboratory of the Chair of Nephrology at the University of Turin, general laboratory of the ASO Giovanni Battista of Turin), by standard laboratory methods. The following parameters were gathered: kidney function data (serum creatinine, urea, creatinine and urea clearances, proteinuria); pancreatic function (glycemic control, glycated hemoglobin, amylases); immunosuppressive drug levels (tacrolimus, cyclosporine A); general data (blood cell counts, liver enzymes, total proteins and albumin levels); virologic controls (cytomegalovirus, herpes virus, Ebstein Barr virus, other viral controls on demand).

The therapeutic schemes (details of major therapeutic changes), the major complications (reported as outpatients and during hospitalization) and the principal therapeutic side-effects (with particular attention to infectious complications) were also gathered from the clinical charts.

Data were extracted by the same operator (Manuel Burdese) and reviewed by the usual caregivers (Maura

Rossetti and Giorgina B. Piccoli). Due to the small number of cases and to the heterogeneity of the patterns, a simple descriptive study design was followed.

Results

Baseline data

The main clinical data at transplant are reported in Table 1. In keeping with the long duration of diabetes (median 28 years, range 21-39 years), all patients displayed at least some diabetes-related comorbidities, albeit with different severity: 6/9 were hypertensive, 8/9 were laser-treated for diabetic retinopathy, only one patient had background retinopathy; of note, she was the youngest of this group and her nephropathy was an unusual, non-diabetes-related one (non-hypertensive nephrosclerosis). Radiological signs of diffuse vascular calcifications were present in 5/9 cases.

Table 1. Baseline data, main data at graft and therapy at discharge

P	Age (yr)	Sex	ESRD	Diab. (yr)	Dial. (mo)	Date of Graft	BMI	Comorbidities	Age donor (yr)	HLA donor	HLA patient	Cold isch. (h)	Hosp. days	Therapy at disch.
1	34	M	DN	21	19	08-17 1999	21.6	Hypertension, retinopathy, neuropathy	19	A 1-2 B 8-18 DR 2-5	A 24-30 B 8-18 DR 3-52	13	17	MP 16 mg FK 10 mg MMF 2 g
2	41	F	DN	28	27	01-19 2000	18.9	Retinopathy, neuropathy, vasculopathy	27	A 3-9 B 12-14 DR 1-8	A 2-10 B 7-21 DR 4-53	6	22	MP 12 mg FK 4 mg MMF 2 g
3	52	M	DN	35	64	02-09 2001	25.1	Hypertension, retinopathy, neuropathy, vasculopathy	34	A 11-9 B 14-21 DR 1-5	A 1-2 B 8-73 DR 3-4	8	42	MP 6 mg FK 5 mg MMF 1 g
4	52	F	DN	29	27	02-18 2001	24.9	Hypertension, retinopathy, neuropathy, psoriasic arthr.	37	A 19-2 B 35-5 DR 6-13	A 2-29 B 12-40 DR 4-7	13	27	MP 10 mg FK 2 mg MMF 1.5 g
5	29	F	NS	25	-	03-04 2001	18.4	Background retinopathy	21	A 10-3 B 18-35 DR 1-3	A 2-3 B 18 DR 6-13	8	30	MP 8 mg FK 3 mg MMF 1.5 g
6	38	M	DN	23	32	03-12 2001	18.3	Retinopathy, neuropathy, vasculopathy, psoriasis	42	A 10-19 B 14-17 DR 1-11	A 2-24 B 44-39 DR 16-8	6	51	MP 8 mg FK 5 mg MMF 2 g
7	37	M	DN	31	32	09-12 2001	24.6	Hypertension, retinopathy, neuropathy, HBV +	18	A 9 B 12-5 DR 4-9	A 2-3 B 5 DR 5-6	9	18	MP 12 mg FK 7 mg MMF 2 g
8	52	M	ND	27	26	04-11 2002	28.0	Hypertension, retinopathy, neuropathy, vasculopathy	35	A 2-11 B 18-35 DR 5-6	A 9-10 B 5-16 DR 3-8	5	25	MP 10 mg FK 8 mg MMF 1.5 g
9	55	F	DN	39	21	02-29 2002	27.0	Hypertension, retinopathy, neuropathy, vasculopathy	45	A 3-9 B 15-7 DR 2-6	A 2-9 B 18-21 DR 3-4	8	25	MP 10 mg FK 13 mg MMF 2 g

Legend: P: patient. M: male. F: female. Age: age at graft in yr. ESRD: end stage renal disease. DN: diabetic nephropathy. NS: non-hypertensive nephrosclerosis. ND: not diagnosed. Diab: diabetes follow-up. BMI: body mass index in kg/m^2. Cold isch: Cold ischemia time in h. Hosp. Days: days of hospitalization. MP: methylprednisolone. FK: tacrolimus. MMF: mycophenolate mophetil (daily doses).

According to the clinical history and to kidney biopsy (performed in 2 cases), the cause of kidney disease was diagnosed as diabetic nephropathy in 7/9. The two cases with "atypical" kidney disease had non-

proteinuric patterns. Three patients also had other autoimmune diseases than type 1 diabetes mellitus, *viz* psoriasis in two, hypothyroidism in one. While the presence of associated autoimmune diseases may suggest a more critical dysfunction of the immune system, this point was not taken into account in the definition and management of the immunosuppressive therapy in these cases.

Early post-transplant follow-up

All kidney allografts produced immediate urinary output; despite the good diuresis, one patient (case 2) experienced delayed graft function, requiring five depurative dialysis sessions. In two cases (patients 8 and 9) delayed pancreatic function occurred, with need for insulin treatment for 24 and 30 days, respectively.

Five patients underwent re-laparotomy in the first month due to acute bleeding (patients 1, 5 and 6) and need for surgical wound revision (patients 3 and 7). One patient (case 6) needed six dialysis sessions after surgery.

Therapeutic schedules and side-effects

All patients received mycophenolate mophetil, tacrolimus and steroids in the induction phase; simulect was employed in 8/9, thymoglobulins were used for patient 1. The basic immunosuppression scheme included i.v. methylprednisolone (500 mg the first day, 200 mg the second and 50 mg the third), followed by either oral methylprednisolone (starting dose 16 mg) or prednisone (starting dose 20 mg) with progressive tapering (targeted at 4 mg or 5 mg at 6 months); tacrolimus levels were set at 12-15 ng/ml in the first trimester, 8-12 ng/ml at 6-12 months and 6-10 ng/ml afterwards. The starting dose of mycophenolate mophetil (MMF) was 2 g/day (Tables 1 and 2).

Table 2. Data at the last update, main reasons for therapeutic changes and main clinical problems

P	Date of graft	Last sCr	Follow-up (mo)	Last therapy	Main problems and reasons for changes
1	08-17-1999	1.0	61	FK 5.0 mg MMF 750.0 mg	Acute post-graft bleeding: surgery. No other problem; slow tapering of immunosuppressors.
2	01-19-2000	1.1	56	FK 5.0 mg MMF 750.0 mg	Delayed graft function with 5 dialysis sessions; surgical removal of cutaneous melanoma (9 months after graft); reduction of immunosuppressors, after surgery; arthritis and aseptic bone necrosis (Charcot joint) in 2002; on that occasion stopped steroids.
3	02-09-2001	1.5	43	FK 5.0 mg MMF 1000.0 mg	Gastro-esophageal reflux and hiatal hernia; pneumonia during hospitalization; gastrointestinal problems; wound diastasis with need for surgical revision; reduction of MMF during hospitalization; CMV infection (1 relapse).
4	02-18-2001	0.8	43	FK 3.5 mg MMF 1000.0 mg	CMV infection; Recurrent acute pyelonephritis (endoscopic correction of VU reflux); surgery for a large abdominal hernia in 2004; small doses of prednisone added on this occasion and slowly tapered. No other problem
5	03-04-2001	1.1	42	FK 7 mg MMF 1000.0 mg	Pre-emptive graft; massive bleeding after graft with need for surgical revision; percutaneous embolization of a pseudo-aneurysm of superior mesenteric artery (15 days after graft). No other problem; slow tapering of immunosuppressors.
6	03-12-2001	4.6	42	FK 1 .0 mg Sirol 2 .0 mg MP 6 .0	Massive bleeding after graft. Reconstruction of arterial anastomosis of the kidney artery; hemoperitomeum, with need for surgical revision; melena; stop MMF and shift to sirolimus 6 months after graft (kidney biopsy); diabetic lesion (right foot) in 2002.
7	09-12-2001	1.1	36	FK 4 .0 mg MMF 750.0 mg	Wound diastasis with need for surgical revision; relapsing CMV infections of long duration (6 months)
8	04-11-2002	5.8 (then dialysis)	20 (then dialysis)	Predialysis: MP 2.5 mg Sirol 6 .0 mg	Suboptimal pancreatic function since start; shift to CyA to improve glycemic control; switch to sirolimus for biopsy-proven chronic nephrotoxicity in October 2003; dialysis re-start in January 2004. Therapy tapered afterwards. Died of cardiovascular accident in June 2004.
9	02-29-2002	0.8	26	MP 2.0 mg FK 5.5 mg MMF 1000.0 mg	Delayed pancreatic function; acute pyelonephritis; elevation of amylase levels of unknown origin, treated by bolus steroids (December 2002), in the hypothesis of initial pancreas rejection.

Legend: P: patient. MP: methylprednisolone. FK: tacrolimus. MMF: Mycophenolate mophetil. sirol: rapamycine (daily doses). Last sCr: last value of serum creatinine.

The first therapeutic reductions were carried out during hospitalization (median duration: 25 days, range 17-51 days), mainly as a result of the various problems occurring in the patients. Generally, MMF was tapered off in cases of viral infections, fever or severe leukopenia. This occurred in four cases. In two cases, MMF was reduced because of early cytomegalovirus infection. In one patient the drug was reduced due to fever of unclear origin and after re-laparotomy for massive bleeding, and in the other because of leukopenia (Tables 1 and 2).

The different doses of corticosteroids at hospital discharge mainly reflect the different durations of hospitalization (Tables 1, 2, and Figure 1). Methylprednisolone doses ranged from 16 mg at hospital discharge in the patient hospitalized for 17 days, to 6 mg at hospital discharge in a patient hospitalized for 42 days. Smaller differences (for example, the patient with the longest hospitalization was discharged with 8 mg methylprednisolone, after 52 days) are due to a slower reduction of corticosteroids in the case of suboptimal function.

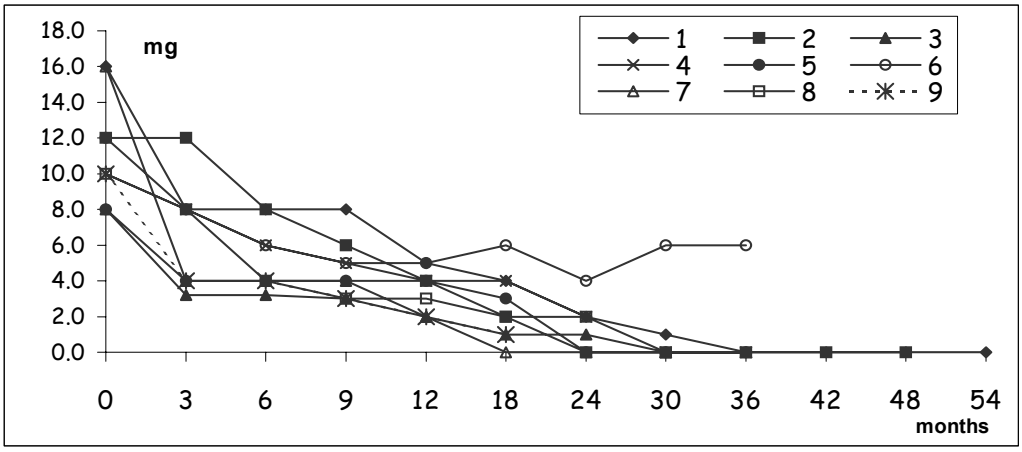


Figure 1. Methylprednisolone oral therapy (mg/day) modifications during the follow-up of the 9 patients. Data since hospital discharge.

The subsequent therapeutic schedules were modulated with the general aim of slowly phasing out of all drugs. Beside the attempt to stop corticosteroids, the indicative "minimal daily doses" were set at 750 mg of MMF and at 5-7 ng/ml of the tacrolimus level. These levels were only indicative and no fixed schedule was followed. The presence of infection problems was one of the main reasons for modulating the therapy, generally considered as an over-immunosuppression state. The biochemical data of the follow-up are reported in Figure 2.

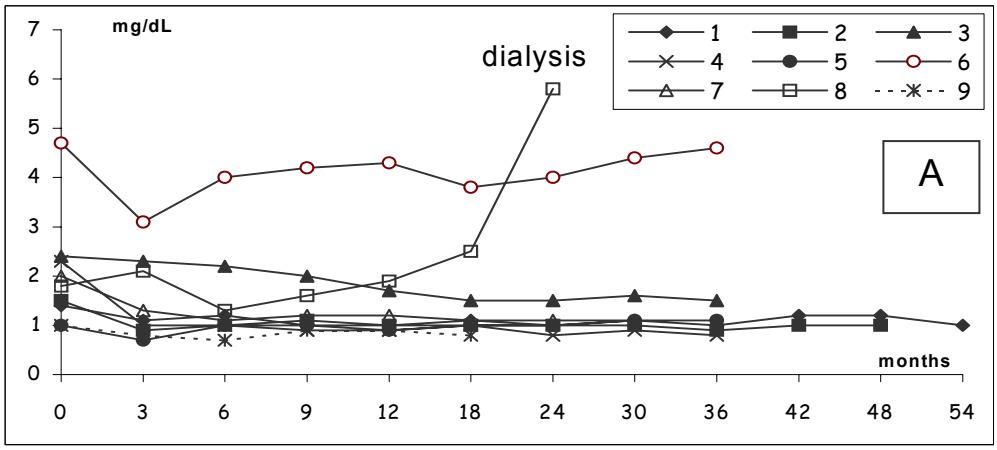
In particular, in case 7, a relapsing cytomegalovirus infection led to a drastic reduction of MMF (from 2 g at hospital discharge, to 750 mg at the 10th month); one patient had a varicella-zoster infection after hospital discharge, and two cases experienced acute graft pyelonephritis (cases 4 and 9, recurrent in case 4).

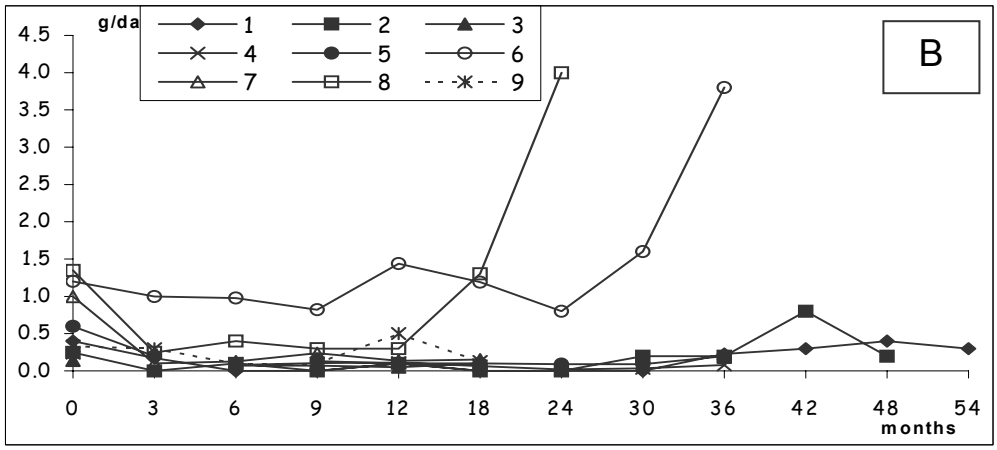
Furthermore, in patient 2, *in situ* melanoma of the left leg was diagnosed 9 months after graft. Even if the neoplasia was presumably present before transplantation, its diagnosis was considered as an indication for further reducing the immunosuppressive therapy.

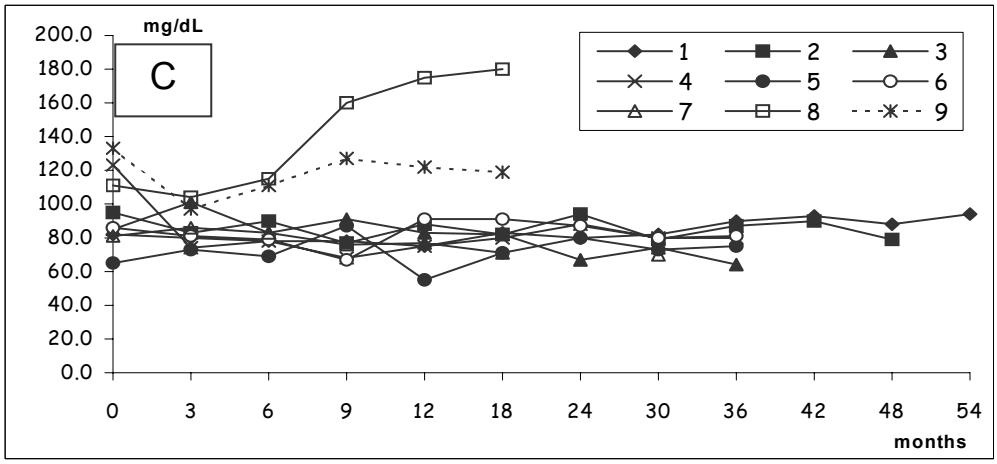
In all but case 6, the stability of kidney and pancreas function after the reduction of immunosuppressive drugs further supported the cautious drug tapering.

Conversely, the occurrence of kidney malfunction was the basis for further therapeutic changes in two cases. Case 6 was switched to rapamycin six months after graft, because of biopsy-proven chronic allograft nephropathy, with vascular involvement. Pancreatic function was always good, while serum creatinine reached 4.6 mg/dl at the last updating, September 2004 (Figure 2). In patient 8, since pancreatic function was suboptimal, tacrolimus was stopped 8 months after graft and cyclosporine A was started, in the hypothesis of a lower diabetogenic effect of the latter. However, in the following 8 months, serum creatinine increased from 1.6-1.9 mg/dl to about 3 mg/dl (Figure 2). A renal biopsy showed signs of chronic calcineurin inhibitor nephrotoxicity (mainly manifest as severe interstitial fibrosis) and a rescue therapy with rapamycin was attempted without success. The patient started dialysis treatment 3 months later and died of an acute cardio-

vascular accident in June 2004. While we suspect that transplant failure may have accelerated his cardiovascular disease, the significance of the immunosuppressive treatment in these situations is difficult to assess. Overall, at the time of this study in September 2004, 6 patients have stopped steroids, while a further one, the last patient grafted in our center, is on treatment with minimal steroid doses (methylprednisolone 2 mg on alternate days) (Tables 1 and 2).







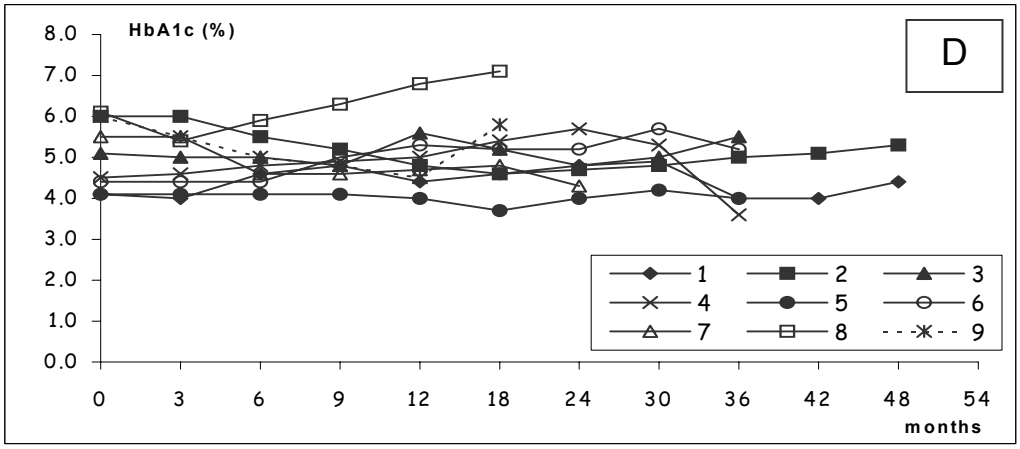


Figure 2. Serum creatinine (**A**), proteinuria (**B**), serum glucose (**C**), HbA1c (**D**) levels during the follow-up in the 9 patients.

Discussion

The studies on non-compliance of regular immunosuppression therapy after kidney transplant incidentally demonstrated that a number of patients may stop this therapy without any serious detrimental effect [11]. It was the development of spontaneous immune tolerance after kidney transplantation that drew our attention to this initially underestimated effect.

The availability of the new generation of more specific immunosuppressive drugs allowed systematic or individually tailored policies of steroid withdrawal currently pursued by several large kidney transplant programs [8, 12]. Such a policy is, however, only seldom proposed in the case of kidney-pancreas transplantation. The limited knowledge of steroid withdrawal therapy suggests that this goal may be accomplished in approximately 50% of recipients [9, 10]. However, further studies are necessary to define the ideal candidates for steroid withdrawal and the long-term impact of steroid avoidance on patient and graft survival and on the evolution of type 1 diabetes-induced complications. The relevance of the results obtained in this study is certainly related to the scarcity of data on this subject and to the fact that this treatment, applied predominantly after kidney transplantation, is studied here in the context of pancreas-kidney transplantation. Our results confirm the positive effects reported on steroid withdrawal in kidney transplantation.

Within the strict limits of the low number of cases, our medium-term case series may underline three practical aspects of potential interest, which may also be seen as points on which discussion can be raised. The first one is the high incidence of infectious diseases, recorded despite a policy of overall low-dose immunosuppression (Table 1). While literature reports a high incidence of infection problems (as high as 35.1 infections per 1000 patient-days) [13], little is known about the policy of decreasing immunosuppression in the presence of infectious diseases and/or after their resolution. Our policy was to maintain overall the decreased doses of immunosuppression in the follow-up, considering infections as a proof of over-immunosuppression. This empirical choice may however be questioned, in particular because of the theoretical risk of triggering an immunologic response by the infectious disease.

The second point is the trial-and-error policy of decreasing the immunosuppressive therapy, with a selection *in itinere*, allowing the patients with good graft function to reduce the drug doses, while keeping the less favorable cases with higher immunosuppressive doses. While the theoretical risk means to exposing the patients to acute or chronic rejection episodes, interestingly, a similar trial-and-error policy has been followed in the newest protocols of tolerance induction. From a speculative point of view, this empirical policy implies a kind of "selection bias" that affects the results in such a way that the low drug doses are the consequence of the good graft function and not vice versa. While effective in clinical practice, such a policy does not allow comparisons among different drug regimens (selection and attrition biases), even on larger scales.

The third point is that, despite all these limits, at least in this very small cohort of patients, tailored steroid withdrawal was possible in selected cases of pan-

creas-kidney grafts in the context of a careful clinical surveillance. While the follow-up is long enough to witness the absence of acute rejection episodes, feared in particular in the first 6-9 months after stopping steroids, the results from our limited study underline the need for further investigation on this issue.

Conclusion

Even if further studies in large cohorts are necessary to define the risks and the benefits of a "minimal" immunosuppressive therapy, our small-scale study may suggest that a tailored immunosuppression policy, more commonly used in the case of kidney transplantation, may also be applied after pancreas-kidney graft. This policy allows steroid withdrawal, at least in selected cases, and may increasingly be followed long-term, when the advantages and good results of pancreas-kidney transplantation become more appreciated. The long-term perspective is to granting a better quality and perhaps also a longer quantity of life for the patients.

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