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Good Results with Individually Adapted Long-Term Immunosuppression Following Alemtuzumab Versus ATG Induction Therapy in Combined Kidney-Pancreas Transplantation: A Single-Center Report

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Statistical Analysis C
Data Interpretation D
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Retrospective analysis of the long-term results of a randomized controlled trial comparing alemtuzumab (ALEM) and antithymocyte globulin (ATG) as induction therapy in simultaneous pancreas-kidney transplantation (SPK) to address individualized long-term immunosuppression.

Between 2006 and 2010 a total of 30 SPKs were randomized to treatment with ALEM plus tacrolimus (TAC) monotherapy (Group A, n=14) versus ATG induction plus TAC, mycophenolate mofetil (MMF) and steroids (Group B, n=16), followed by individualized long-term immunosuppression. We here present the long-term results for graft survival, graft function, and major complications.

The 9-year patient survival rates in Groups A and Group B were 92.9% and 86.7% respectively; pancreas graft survival was 75.0% and 65.0% respectively; renal graft survival was 83.1% and 93.8% respectively. Long-term graft function was excellent with a creatinine of 1.5 mg/dL and 1.4 mg/dL, fasting glycemia of 104 mg/dL and 102 mg/dL, hemoglobin (Hb) A1c of 5.4 g% and 5.6 g% in Group A and Group B, respectively. Major complications were comparable in both groups.

Good long-term results for patient, pancreas graft and kidney graft survival were achieved in both groups with individually adapted maintenance immunosuppression. ALEM is a valid induction therapy.

MeSH Keywords: **Immunosuppressive Agents • Kidney Transplantation • Pancreas Transplantation**

Abbreviations: **ALEM** – alemtuzumab; **ATG** – anti-thymocyte globulin; **BK-nephropathy** – polyomavirus nephropathy; **CIT** – cold ischemia time; **CRP** – C-reactive protein; **CT** – computed tomography; **CyA** – cyclosporine A; **EUR** – Euro; **FSGS** – focal segmental glomerulosclerosis; **HLA** – human leukocyte antigen; **ICB** – intracerebral bleeding; **INF** – initial non-function; **IV** – intravenous; **MM** – mismatch; **MMF** – mycophenolate mofetil; **MPA** – mycophenolate acid; **PRA** – panel-reactive antibodies; **PTCA** – percutaneous transluminal coronary angioplasty; **PTT** – partial thromboplastin time; **ReTX** – retransplantation; **SD** – standard deviation; **SPK** – simultaneous pancreas-kidney transplantation; **TAC** – tacrolimus; **x-ray** – radiography

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Background

Improved patient and graft survival in simultaneous pancreas-kidney transplantation (SPK) can be achieved with induction therapy [1–6]. Controlled trials comparing the anti-CD52 antibody alemtuzumab (ALEM) and anti-thymocyte globulin (ATG) in SPK report good results for ALEM [7–13]. In contrast to the Euro-SPK study including ATG, reports on long-term outcome in SPK with ALEM remain sparse and long-term immunosuppressive treatment following initial protocol-based therapy has not been addressed [12–15].

We previously published the 1-year results of a single-center prospective randomized trial comparing ALEM induction plus tacrolimus (TAC) monotherapy (n=14) versus ATG followed by TAC plus mycophenolate mofetil (MMF) and steroids (n=16) in SPK with comparable results [11]. We here analyze the long-term results regarding immunosuppression, patient/graft survival, long-term function, major complications.

Material and Methods

We retrospectively investigated the long-term outcome in patients formerly enrolled in a prospective randomized trial (EudraCT: 2006-000845-21; demographic data: Table 1).

Surgical procedures were performed according to standard techniques, routine controls (after month 12) 3 to 6 weeks, renal biopsies in deteriorated graft function, endoscopic inspections and/or computed tomography (CT) angiography of the duodenal graft for suspected rejection or bleeding.

Statistical methods

The *t*-test and descriptive analysis: applied for data assessment. Patient and graft survivals were analyzed using Kaplan-Meier method and SPSS (version 22) used for statistical analysis.

The analysis was approved by the local ethics committee.

Results

After a mean observation time of 9.5 years (6.3–9.9 years), the 5-year and 9-year patient survival in Group A was 92.9% and 92.9% respectively, in Group B the 5-year and 9-year survival was 100% and 86.7% respectively (*P*=0.666). The 5-year and 9-year renal graft survival (censored for death) in Group A was 92.3% and 83.1% respectively, in Group B, the 5-year and 9-year survival was 93.8% and 93.8% respectively (*P*=0.954). The reasons that 2 renal grafts were lost in Group A were primary non-function and chronic rejection at month 1 and 13,

Table 1. Demographic data and graft function parameters concerning patients (censored for death) with long-term functioning kidney or pancreas graft, respectively, at date of last follow-up.

		Group A n=14	Group B n=16	*P* value
Female		3 (21%)	2 (12%)	0.53
Age (years)		45±7	43±9	0.46
Diabetes Type I		13 (93%)	16 (100%)	0.28
PRA-negative (n patients)		13	15	
PRA-positive (n patients)		1 (PRA 28%)	1 (PRA 4%)	
Donor age (years)		30±12	32±11	0.74
HLA	MM AB	1.4±2.2	1.5±0.5	0.67
	MM DR	1.5±0.5	1.4±0.5	0.18
CIT (hours)	Kidney	11±3	10±4	0.70
	Pancreas	13±3	12±3	0.31
Long-term vital kidney grafts		**9/14**	**10/16**	
Creatinine mean (mg/dL)		1.5 (SD.52)	1.4 (SD.71)	
Long-term vital pancreatic grafts		**9/14**	**11/16**	
Glucose (mg/dL, fasting)		103.75 (SD 29.71)	102.1 (SD 29.31)	
HbA1c (g%)		5.4 (SD.56)	5.6 (SD.79)	
Insulin-free (n patients)		9	11	

CIT – cold ischemia time; HLA – human leukocyte antigen; MM – mismatch; PRA – panel-reactive antibodies.

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Table 2. Causes of death and major complications.

	Group A	Group B	*P* value
Causes of death			
Sepsis	1 (month 22)		
Intracerebral bleeding		1 (month 59)	
Lung cancer	1 (month 50)		
Unknown		1 (month 60)	
Major complications			
Peripheral angiopathy requiring intervention (n total)	6	1	
Digital amputation	3	0	
Leg amputation	2	0	
Vascular dilatation	1	1	
Cerebrovascular ischemia	2	0	
Cerebrovascular bleeding	1 (fatal)	0	
Coronary heart disease requiring revascularization	2	1	
Arterial bleeding pancreas graft	1 (graft loss)	0	
Hemolytic anemia (splenectomy)	1	0	
Portal vein thrombosis (partial)	0	1	
Persistent leukopenia	0	1	
Idiopathic thrombopenia	1	0	
Tumor total	**1**	**3**	**0.6**
Lung cancer (year 3)	1 (fatal)		
B cell lymphoma (year 6*; liver; rituximab+CHOP)		1	
Prostate cancer (year 8*, same patient)		1	
Cervix cancer (year 8, conisation)		1	
Severe infectious complications			
Sepsis	1 (fatal)	0	
Pneumonia	1	0	
Bacteremia	1	0	
Tuberculosis	1	0	
Recurrent cystitis	1	0	
Osteomyelitis	0	1	
Polyomavirus nephropathy	0	1	
Recurrent condylomata	0	1	
Hepatitis B	0	1	
Total	**5**	**4**	

respectively. In Group B there were 2 grafts lost, one because of focal segmental glomerulosclerosis at month 95 and one because of chronic rejection at month 99.

The 5-year and 9-year pancreas graft survival (=insulin-free) in Group A was 92.9% and 75.0% respectively. In Group B, the 5-year and 9-year pancreas graft survival was 81.3% and 65.0% respectively (*P*=0.656). In Group A, the 3 pancreatic grafts were lost due to venous thrombosis, chronic rejection, and bleeding at month 1, month 70, and month 95 respectively. In Group B, the 3 cases were lost to venous thrombosis, 2 at month 1 and 1 at month 49), and 1 case was lost to chronic rejection at year 9; chronic rejection was clinically suspected upon functional deterioration and impaired organ perfusion (CT scan).

Lymphocytes absolute in Group A and Group B were mean 1.61 G/L and 1.7 G/L respectively, and leucocytes in Group A and Group B were 5.4 G/L and 6.1 G/L respectively (see Table 1 for laboratory values in functioning grafts). One case of fatal lung cancer occurred in Group A, and 3 cases survived malignancies in Group B (see Table 2 for causes of death and major complications). Long-term immunosuppression in patients with both functioning grafts in Group A was TAC monotherapy (n=3), CyA monotherapy (1; TAC-associated idiopathic thrombopenia), TAC plus prednisolone (1; TAC decreased due to nephrotoxicity), TAC plus azathioprine (2; acute kidney rejection at year 1).

Conversions in Group B

Three conversions to TAC monotherapy (BK virus nephropathy (at year 2), leukopenia (at 2 year), osteomyelitis (at year 7), 2 from MMF to MPA/azathioprine (diarrhea at year 1), 1 from TAC to CyA (drug fever at year 1). No acute rejections occurred in either group after month 12. Apart from 1 patient in Group A, all patients in both groups are steroid-free. ALEM was less expensive than ATG (difference EUR 1178.-); MMF (annual costs EUR 3330.-) was not administered in the ALEM Group.

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Discussion

ALEM, currently used mainly for the treatment of multiple sclerosis, previously developed as an effective lymphocyte-depleting agent in renal transplantation, is considered effective as induction agent in SPK with results comparable to those for ATG [7–13]. However, little is known about the long-term results [7–13,16,17].

TAC is preferred for maintenance immunosuppression following ALEM induction therapy, since T cells with a memory-like phenotype are dominant following T cell depletion, but sensitive to calcineurin inhibitors [7–11,13,18,19]. Hesitation concerning increased use of ALEM was fueled by contrasting reports about the immunological benefit. A predominance of CD4 memory cells, T memory cells, regulatory B and T cells together with an increase in donor-specific antibodies, perivascular C3d deposits, vasculopathy and fibrosis following exposure to ALEM, indicate a diverse effect [20–23].

We retrospectively analyzed the 9-year outcome of patients previously enrolled in our 1-year prospective randomized trial comparing ALEM and ATG, which was logically performed as ALEM was not included in the important multicenter study Euro-SPK [11,15]. The ALEM dosage 30 mg intravenous was based on our own renal transplantation center study [11,24]. ATG Fresenius 8 mg/kg intraoperatively was preferred in order to take into consideration infection risks from 3 daily doses of 4 mg/kg following intraoperative application (Euro SPK study) and a reported rejection rate of 34.5% within ATG 4–6 mg/kg in renal transplantation [15,25].

The 5-year and 9-year pancreas graft survival rates of 92.9% and 75% respectively in the ALEM Group and 81.3% and 65% respectively in the ATG Group compare favorably with long-term results from registries and high-volume centers [1,2,4,6]. While we are aware of the limitations of our small cohort and the various long-term immunosuppression administered, we observed no increased rate of chronic rejection in our ALEM patients, probably related to the good graft quality of usually younger pancreas donors and the close clinical follow-up, resulting in early adapted maintenance immunosuppression, the majority in both groups steroid-free.

Reasonable flexibility with regard to maintenance immunosuppression seems advantageous concerning adherence [14]. The long-term function of the surviving pancreatic grafts is convincing since all patients are insulin-free. No significant difference was observed regarding major complications or malignancies, corresponding to Puttarajappa et al. reporting no increased cancer incidence with ALEM in renal transplantation [26]. Costs of ALEM versus ATG differed since MMF was not administered in the ALEM Group, eventually levelling out during the long-term adapted immunosuppression. ALEM was less expensive than ATG. Regarding reported early lymphocyte counts of mean 2.6% with ALEM, we observed normal lymphocyte counts in both groups at 9.5 years [27].

Conclusions

Although no strong conclusion can be drawn regarding the superiority of either induction regimen, the particular valence of this relatively small retrospective study is its well documented real-world experience. Our findings, however, indicate that ALEM is a valid induction therapy and individualized immunosuppression according to the clinical course is the treatment of choice.

Conflict of interest

None.

Units of measurement

Cyclosporine A level: ng/mL; Glucose: mg/dL; Granulocyte-stimulating agent: million units; HbA1c: g%; Leukocytes: G/L; Lymphocytes absolute: G/; PRA: %; PTT value: "(seconds); Serum creatinine: mg/dL; Tacrolimus level: ng/mL.

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