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Impact of HLA matching on the outcome of simultaneous pancreas–kidney transplantation

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Abstract

Background. Simultaneous pancreas–kidney (SPK) transplantation has become the therapy of choice for type 1 diabetic patients with end-stage renal disease. The current analysis examined the impact of human leukocyte antigen (HLA) matching on graft outcome following SPK transplantation. The study population was obtained from patients enrolled in the Euro-SPK 001 study.

Methods. The effect of HLA matching on graft function and survival was assessed in 180 SPK recipients in whom complete donor–recipient HLA data were available. A group of 45 patients with 0–3 HLA mismatches (MM) was compared with a group of 135 patients with 4–6 MM.

Results. There were no differences in 3-year kidney, pancreas or patient survival between the 0–3 and 4–6 MM groups. Biological parameters of kidney and pancreas graft function were similar in both groups. Significantly more patients with 0–3 MM (66%) were rejection-free at 3 years than was the case among those with 4–6 MM (41%; $P = 0.003$). The relative risk of acute rejection was 2.6 times higher among patients with 4–6 MM than among those with 0–3 MM.

Conclusions. There was no evidence that HLA matching was associated with improved kidney or pancreas survival. However, a higher rate of acute rejection was observed with poor HLA match, which may impact long-term survival.

Keywords: graft survival; HLA matching; kidney–pancreas transplantation; multicentre study; prospective study; rejection

Introduction

Simultaneous pancreas–kidney (SPK) transplantation is the only treatment that can consistently establish, on a large scale, freedom from dialysis and an insulin-independent, euglycaemic state in uraemic patients with type 1 insulin-dependent diabetes mellitus [1]. The current success with this procedure is reflected in its 1-year patient survival rates of ~95% and 1-year pancreatic graft survival rates in excess of 80% [2]. These excellent survival rates are the result of improved donor and recipient selection criteria, refined surgical techniques, better immunosuppressive protocols and improved pre- and post-operative care [3–5].

The major histocompatibility system [human leukocyte antigen (HLA) in man] has several functions, including graft immunogenicity and host response, disease susceptibility and cell co-operation in immune responses. Registry data from both the Collaborative Transplant Study and United Network for Organ Sharing (UNOS) have demonstrated a strong positive effect of HLA matching on the outcome of kidney transplantation [6,7]. In pancreas transplantation, however, the question of HLA matching is confounded by the hypothesis that the outcome may be worse in patients receiving a DR-identical graft, since certain DR antigens are associated with susceptibility to diabetes and also because autoantigen recognition is undertaken in a major histocompatibility complex (MHC)-restricted fashion [8].

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The present analysis of the Euro-SPK 001 study was undertaken to evaluate the potential effect of good HLA matching on the outcome of SPK transplantation using modern immunosuppressive regimens based on tacrolimus or cyclosporin microemulsion (ME).

Patients and methods

Study design

The overall objectives, methods and design of the Euro-SPK 001 study have been described in full previously [9] and also elsewhere in this supplement (Saudek F *et al.*). A brief synopsis is given below.

A total of 205 SPK transplant patients with end-stage, C-peptide-negative, type 1 diabetic nephropathy were recruited into the study from 10 centres in Europe and one centre in Israel. All patients received quadruple immunosuppressive therapy based on either tacrolimus ($n = 103$) or cyclosporin-ME ($n = 102$), given with mycophenolate mofetil (MMF), corticosteroids and antibody induction therapy (rabbit anti-thymocyte globulin). The initial oral daily dose of tacrolimus was 0.2 mg/kg, with subsequent doses adjusted to target whole-blood trough levels in the range 8–15 ng/ml by day 5 post-transplant. The recommended initial oral daily dose of cyclosporin-ME was 7 mg/kg, adjusted to target whole-blood trough levels of 150–250 ng/ml by day 5. Corticosteroid therapy was progressively withdrawn from all patients between 3 and 6 months post-transplantation.

HLA typing

HLA typing was undertaken individually at each centre. Only broad antigens were taken into account for the donor–recipient HLA matching. The three centres that had specific HLA matching criteria accepted grafts from donors with at least one HLA-DR match and one HLA-A and/or HLA-B match (15 patients). None of the other centres had an HLA matching policy.

Diagnosis of rejection and graft failure

In the majority of cases, rejection was diagnosed on the basis of a renal transplant biopsy, although a diagnosis of acute rejection was occasionally obtained empirically by response to anti-rejection treatment in the absence of biopsy. Renal graft failure was defined as a permanent return to haemodialysis, and pancreatic graft failure was defined as a permanent return to insulin therapy. Death with a functioning graft was included as graft failure.

Statistical analysis

Statistical analyses were undertaken using the STATISTICA software package (StatSoft, Tulsa, USA). The χ^2 and Fisher's exact tests were used to compare categorical variables. The Mann–Whitney U-test was used for continuous variables. Survival rates and time-dependent variable rates were estimated using the Kaplan–Meier method and were compared using the log-rank test. Exploratory analyses were undertaken using Cox multivariate regression analyses. $P < 0.05$ was considered to be statistically significant. Mean values are expressed with SDs.

Results

Analysis of HLA matching

HLA typing was available for 181 donors (88.3%) and 184 recipients (89.8%). Complete HLA data for both donor and recipient were available for 180 (87.8%) transplants (90 in each treatment group). As shown in Table 1, both treatment arms were comparable with respect to HLA matching, with no statistically significant differences between the tacrolimus and cyclosporin-ME groups with regards to class I, class II and combined class I and II matching data.

Because of their similar size and HLA-matching distribution, data from the tacrolimus and cyclosporin-ME groups were pooled for further analysis. The influence of HLA matching was studied by comparing outcomes in patients with 0–3 HLA mismatches (MM) ($n = 45$) and 4–6 MM ($n = 135$). As shown in Table 2, the demographic data were similar in the two MM groups, except for significant differences in donor age, higher in the 0–3 MM group than in the 4–6 MM group (31.8 *vs* 28.5 years, respectively; $P = 0.046$), and kidney ischaemic time, which was longer in the 0–3 MM group (13 h and 13 min *vs* 11 h and 36 min; $P = 0.047$).

Table 1. Number of HLA mismatches in 180 recipients of SPK transplants

	No. (%) of patients		
	Tacrolimus ($n = 90$)	Cyclosporin-ME ($n = 90$)	Total ($n = 180$)
Class I			
A 0–1	60 (67)	55 (61)	115 (64)
A 2	30 (33)	35 (39)	65 (36)
B 0–1	34 (38)	40 (44)	74 (41)
B 2	56 (62)	50 (56)	106 (59)
AB 0–2	29 (32)	31 (34)	60 (33)
AB 3–4	61 (68)	59 (66)	120 (67)
Class II			
DR 0	7 (8)	8 (9)	15 (8)
DR 0–1	51 (57)	48 (53)	99 (55)
DR 2	39 (43)	42 (47)	81 (45)
Class I and II			
ABDR 0	0	1 (1)	1 (<1)
ABDR 1	1 (1)	3 (3)	4 (2)
ABDR 2	4 (4)	3 (3)	7 (4)
ABDR 3	19 (21)	14 (16)	33 (18)
ABDR 4	31 (34)	36 (40)	67 (37)
ABDR 5	26 (29)	23 (26)	49 (27)
ABDR 6	9 (10)	10 (11)	19 (11)

HLA = human leukocyte antigen; SPK = simultaneous pancreas–kidney; cyclosporin-ME = cyclosporin microemulsion.

Table 2. Demographic data and graft characteristics according to HLA mismatch (MM) in 180 SPK transplant procedures

	0–3 MM ($n=45$)	4–6 MM ($n=135$)
Mean donor age (years)	31.8 ± 9.8	28.5 ± 11.0[a]
Mean recipient age (years)	40.1 ± 5.2	39.5 ± 7.4
Sex ratio F/M	17/28	48/86
PRA >5% [*n* (%)]	3 (6.7)	11 (8.1)
Recipient BMI (kg/m^2)	23.4 ± 2.7	23.0 ± 3.0
Pancreatic ischaemic time (h:min)	12:21 ± 5:12	10:56 ± 4:58
Kidney ischaemic time (h:min)	13:13 ± 4:58	11:36 ± 4:47[a]
Pancreatic GVE [*n* (%)][b]	21 (46.7)	70 (51.9)

SPK = simultaneous pancreas–kidney; PRA = panel-reactive antibody; BMI = body mass index; GVE = graft vessel extension.
[a]$P<0.05$ *vs* 0–3 MM.
[b]GVE is used if the donor vein or artery is too short to be anastomosed directly to the recipient's vessel.

Table 3. Influence of HLA mismatch (MM) on graft and patient survival following SPK transplantation

	Survival (%)	
	0–3 MM ($n=45$)	4–6 MM ($n=135$)
Pancreas		
1 year	88.9	80.7
3 years	84.3	76.9
Kidney		
1 year	95.6	94.1
3 years	95.6	91.6
Patient		
1 year	100	98.5
3 years	97.7	96.2

SPK = simultaneous pancreas–kidney; HLA = human leukocyte antigen.

Graft and patient survival

Details of graft and patient survival are summarized in Table 3. Overall pancreas survival and kidney survival were 82.9 and 93.7%, respectively, at 1 year post-transplant, 79.5 and 92.7% at 2 years, and 79.0 and 91.2% at 3 years. No differences in actuarial survival rates between the two MM groups were seen for either pancreatic ($P=0.29$) or kidney graft survival ($P=0.65$). Likewise, there were no significant differences between the two groups in terms of actuarial patient survival rates ($P=0.62$). Overall patient survival was 97.6% at 1 year, 96.6% at 2 years and 96.1% at 3 years post-transplant.

Corticosteroid withdrawal

Corticosteroid withdrawal at month 6 and years 1, 2 and 3 post-transplant was achieved in nine, 17, 18 and 18 patients, respectively, in the 0–3 MM group and in 23, 45, 64 and 66 patients in the 4–6 MM group. No statistically significant difference in the actuarial rate of corticosteroid withdrawal was observed between the two groups.

Graft function and acute rejection

As shown in Table 4, biochemical indices of kidney and pancreatic function were comparable in the 0–3 MM and 4–6 MM groups during the 3-year study. However, the rejection-free actuarial survival rate was significantly higher in the 0–3 MM group than in the 4–6 MM group (66.4 *vs* 41.1%, respectively; $P=0.003$; Figure 1). Cox multivariate regression analysis showed that the relative risk of rejection was 2.6 times higher among patients with 4–6 MM than among those with 0–3 MM ($P=0.003$).

At the 3-year follow-up, 15 (33%) patients in the 0–3 MM group had at least one clinical or biopsy-proven rejection episode compared with 77 (57%) patients in the 4–6 MM group ($P=0.006$). The difference was also statistically significant for biopsy-proven rejection episodes only ($P=0.01$). In the 0–3 MM group, there were nine biopsy-proven acute rejection episodes (20%), including three moderate or severe episodes, compared with 55 episodes (41%) of biopsy-proven acute rejection in the 4–6 MM group, which included 10 moderate or severe episodes.

Ten (67%) patients in the 0–3 MM group had a single episode of rejection and five (33%) had multiple episodes. This was similar to the experience in the 4–6 MM group, in which 43 (56%) patients had a single episode and 34 (44%) had multiple episodes.

Total HLA-DR MM did not appear to influence the severity of the first biopsy-proven rejection episode. Among 15 patients with no DR MM, two (13%) had borderline or mild rejection and two (13%) had moderate or severe rejection. Among 84 patients with one DR MM, 23 (27%) had borderline or mild rejection and four (5%) had moderate or severe episodes. Similar proportions were found among 81 patients with two DR MM: 26 (32%) had borderline or mild and seven (9%) had moderate or severe rejection episodes.

Effect of DR3 and DR4 matching

DR3 or DR4 HLA antigens were found in 171 out of 187 (91%) transplanted patients; donor HLA antigens were DR3 or DR4 in 38% (70 out of 182) of cases. At the 3-year follow-up, there was no significant difference in the rate of pancreatic graft loss among the DR3/4 recipients (32 out of 171; 19%) and the other DR recipients (three out of 16; 19%). Among the 180 patients for whom donor–recipient HLA matching was known, 67 HLA-DR3 or DR4 patients received a HLA-DR3 or DR4 donor organ; 13 of the 67 (19%) patients had lost their pancreas by 3 years post-transplant. Similarly, in the 113 non-HLA-DR3 or -DR4-matched donor–recipient patients, 22 (19%) had lost their pancreas by 3 years. In addition, no statistically significant differences at 1, 2 or 3 years post-transplant were observed in

Table 4. Biochemical indices of kidney and pancreatic graft function according to HLA mismatch (MM) in 180 SPK transplant procedures

	0–3 MM ($n=45$)			4–6 MM ($n=135$)		
	Year 1	Year 2	Year 3	Year 1	Year 2	Year 3
Creatinine clearance (ml/min)	65 ± 17 ($n=38$)	67 ± 18 ($n=36$)	64 ± 16 ($n=34$)	67 ± 21 ($n=120$)	67 ± 22 ($n=112$)	65 ± 25 ($n=91$)
Serum creatinine (mg/dl)	1.4 ± 0.3 ($n=38$)	1.5 ± 0.5 ($n=38$)	1.5 ± 0.4 ($n=37$)	1.4 ± 0.5 ($n=120$)	1.5 ± 0.7 ($n=116$)	1.6 ± 0.9 ($n=107$)
Fasting glucose (mg/dl)	91 ± 14 ($n=33$)	89 ± 13 ($n=32$)	89 ± 17 ($n=31$)	91 ± 33 ($n=99$)	90 ± 18 ($n=96$)	91 ± 33 ($n=83$)
Fasting C-peptide (ng/ml)	3.1 ± 1.0 ($n=21$)	3.3 ± 1.3 ($n=21$)	3.0 ± 1.5 ($n=18$)	3.7 ± 2.4 ($n=47$)	3.5 ± 2.1 ($n=47$)	2.4 ± 1.4 ($n=38$)
HbA_{1C} (%)	5.6 ± 0.8 ($n=30$)	5.3 ± 0.7 ($n=31$)	5.2 ± 0.8 ($n=31$)	5.5 ± 1.1 ($n=90$)	5.4 ± 0.7 ($n=97$)	5.2 ± 0.7 ($n=82$)

HLA = human leukocyte antigen; SPK = simultaneous pancreas–kidney; HbA_{1c} = glycosylated haemoglobin.

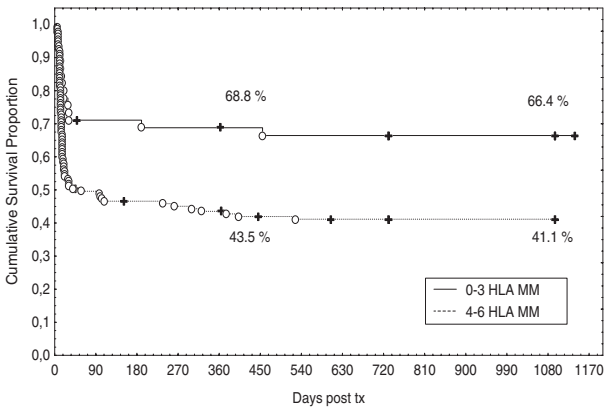

Fig. 1. Influence of HLA mismatch (MM) on rejection-free survival following simultaneous pancreas–kidney transplantation. Rejection-free survival was significantly higher with 0–3 M *vs* 4–6 MM ($P=0.003$, Kaplan–Meier analysis). ○ = rejection episode; + = censored.

biochemical indices of kidney and pancreatic function in organs harvested from DR3/4 donors *vs* non-DR3/4 donors (Table 5).

Discussion

The analysis presented here examines the effect of HLA matching on the outcome of 180 SPK transplantation procedures in a prospective, randomized, multicentre study primarily designed to compare two immunosuppressive regimens based on tacrolimus and cyclosporin-ME. For purposes of comparison, two unequal groups of patients were analysed, 25% having 0–3 HLA MM and 75% having 4–6 HLA MM. With a completed 3-year follow-up for all patients, there was no evidence to support a beneficial impact of HLA matching in terms of patient survival, and pancreatic and kidney graft survival. In addition, there were no differences between the MM groups with respect to metabolic function of the transplanted grafts in terms of creatinine clearance, glycosylated haemoglobin and fasting blood glucose. There was, however, a significantly lower rate of acute rejection in the patient group with the superior HLA match. Although our study showed no impact of this result on kidney survival, a lower incidence of acute rejection may be of importance given the relationship between acute kidney rejection in the first year post-transplant and long-term kidney graft loss [10].

The value of HLA matching in kidney transplantation and its association with prolonged graft survival is well recognized [6,7]. Accordingly, most organ-sharing organizations give priority to kidney recipients with a high degree of matching. Most studies of HLA matching in SPK transplantation have looked only at its effects on pancreas survival, but, in one large SPK transplantation series from the UNOS registry, no significant benefit of HLA matching on kidney survival could be established [11]. Despite this, actuarial kidney graft survival assessed at 8 years post-transplantation was found to increase in parallel to the number of overall HLA matches. Statistical significance could not be demonstrated due to the small number of patients (6%) with an HLA match >3 [11]. Achieving significant differences in graft survival in our trial may also have been hampered by a relatively small study population.

The value of HLA matching in pancreas transplantation has evolved over the last 15 years in parallel with advances in both surgical techniques and immunosuppression, which have led to improved clinical outcomes [12,13]. These advances appear to have masked the potential beneficial effect of HLA matching in pancreas graft survival. The first analysis of the benefits of HLA matching in pancreas transplantation was published in 1988, using data from the International Pancreas Transplant Registry (IPTR). In 380 technically successful cases transplanted between 1966 and 1987, an HLA match of ≥4 antigens was associated with a significantly higher 1-year pancreas graft survival than an HLA match ≤3 (66 *vs* 54%, respectively; $P=0.038$) [14]. The overall 1-year graft survival rates were 49 and 39%, respectively. Two single-centre series from the early 1990s (Minneapolis

Table 5. Biochemical indices of kidney and pancreatic graft function according to DR allele

	DR3/DR4 donors ($n=70$)			Other DR donors ($n=112$)		
	Year 1	Year 2	Year 3	Year 1	Year 2	Year 3
Creatinine clearance (ml/min)	65 ± 19 ($n=62$)	69 ± 21 ($n=53$)	65 ± 17 ($n=45$)	69 ± 21 ($n=98$)	67 ± 21 ($n=97$)	65 ± 25 ($n=81$)
Serum creatinine (mg/dl)	1.4 ± 0.4 ($n=62$)	1.4 ± 0.6 ($n=56$)	1.5 ± 0.7 ($n=53$)	1.4 ± 0.5 ($n=98$)	1.5 ± 0.7 ($n=100$)	1.6 ± 0.9 ($n=93$)
Fasting glucose (mg/dl)	94 ± 42 ($n=53$)	87 ± 12 ($n=48$)	88 ± 17 ($n=41$)	89 ± 16 ($n=81$)	92 ± 19 ($n=81$)	91 ± 34 ($n=75$)
Fasting C-peptide (ng/ml)	3.4 ± 1.6 ($n=30$)	3.1 ± 1.3 ($n=29$)	3.0 ± 1.9 ($n=21$)	3.6 ± 2.4 ($n=40$)	3.7 ± 2.2 ($n=39$)	2.4 ± 1.0 ($n=35$)
HbA_{1C} (%)	5.5 ± 1.3 ($n=51$)	5.3 ± 0.7 ($n=50$)	5.2 ± 0.8 ($n=43$)	5.5 ± 0.7 ($n=71$)	5.4 ± 0.6 ($n=80$)	5.2 ± 0.7 ($n=72$)

SPK = simultaneous pancreas–kidney; HbA_{1c} = glycosylated haemoglobin.

and Madison groups) confirmed these observations, reporting a significant impact of HLA-DR matching [15–17]. In addition, a prospective, European multicentre study ($n=62$), also from the early 1990s, reported a beneficial effect of HLA-DR matching, but not of HLA-A or -B matching, on pancreas survival, with an overall 1-year graft survival rate of 67% [18]. In contrast, however, an analysis of UNOS data, which included >3000 transplantations undertaken in 1988–1994, showed no benefit of HLA matching on pancreas graft survival, and reported overall graft survival rates of 85% at 1 year and 75% at 5 years [11]. Although the issue of small patient populations remains, no consistent increase in pancreas graft survival could be related to HLA matching, even in the relatively large UNOS study [11]. The results of our own study, in which we achieved a 1-year pancreas graft survival rate of 83%, concur with the most recent observations.

The evolution of the impact of HLA matching on pancreas survival is well illustrated in a second IPTR study, in which results from the 1987–1994 era were compared with those from the 1995–2000 era [19]. In contrast to the findings of the European study, no effect of HLA-DR matching was observed. However, in the early era (1987–1994), a significant beneficial effect of HLA-A and -B matching was found for pancreas after kidney (PAK) transplantation and pancreas transplantation alone (PTA) procedures as opposed to SPK. This effect persisted in the later era, but was no longer statistically significant because overall outcomes of pancreas transplantation had improved markedly [19]. Of note, pancreas survival has traditionally been less favourable with the PAK and PTA procedures, primarily due to difficulties in diagnosing rejection, compared with the SPK procedure with which rejection episodes are readily diagnosed from kidney biopsies. Despite this, the IPTR findings suggest that advances in immunosuppression have closed the gap in success rates between PTA/PAK and SPK techniques.

It is important that any discussion on HLA matching in SPK transplantation focuses on its feasibility as well as its benefits. Donor selection criteria for whole-organ pancreas transplantation are more stringent than for other abdominal organs. As a result, in the Eurotransplant and UNOS areas, pancreatic tissue is procured from only 18–22% of all cadaveric donors [20,21]. The apparent shortage of available organs makes it difficult to match for donor and recipient HLA compatibility. In the UNOS study described previously [11], fewer than 6% of recipients had a >3 HLA antigen match, while 56% had zero or one HLA match. One way of overcoming the difficulties in HLA matching of donors with recipients is to attempt to match HLA cross-reactive groups (CREGs). These are groups of HLA antigens that exhibit limited polymorphism and share common amino acid sequences, enabling them to cross-react with specific antibodies. The impact of CREG matching on pancreas graft survival was evaluated in a recent IPTR registry analysis of 4896 transplants [22]. Results showed that improved outcome was only achieved in the PAK and PTA categories. The impact of CREG matching in kidney transplantation, however, has been a matter of controversy between centres in Europe and the USA. North American registry studies have reported improved outcome, allocation and reduced HLA sensitization [23,24], but this has not been the experience in Europe [25]. One possibility is that the regional differences are related to the higher ethnic disparities in the North American population.

The current era of highly efficient immunosuppressive therapies may have unfolded a shift in the balance between the benefits and detriments of HLA matching. Certain HLA antigens, such as DR3 and DR4, are prevalent in the type 1 diabetic population [8]. In our study, 91% of recipients expressed DR3 or DR4 antigens, compared with 38% of the donor population. However, there is no evidence to suggest that a DR3/DR4 pancreas is more likely to induce recurrence of type 1 diabetes in a patient receiving immunosuppressive therapy. Accordingly, we observed no impact of DR3/DR4 matching on graft survival.

Perhaps more importantly, there is increasing evidence from animal models of autoimmune diabetes and islet transplantation that β-cell destruction is mediated by MHC-restricted effector mechanisms [26,27].

In other words, autoantigen presentation might be more effective in an MHC-matched context. If these observations apply to the human situation, it may imply that HLA matching is not desirable for islet or pancreas transplantation in patients with type 1 diabetes. This may explain why the association between HLA matching and better kidney survival is not observed for pancreas survival.

In summary, the current analysis of data from the Euro-SPK 001 study showed no advantage of HLA matching in the 3-year patient, kidney graft and pancreas graft survival rates. A lower rate of acute kidney rejection was seen when the HLA match was >3. This observation may have longer-term implications with respect to improved graft half-life. However, in the absence of demonstrable benefits in graft survival, and because of feasibility issues, HLA matching is currently recommended only for SPK recipients thought to be at risk of rejection.

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Conflict of interest statement. None declared.

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