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Is HLA matching relevant in pancreas transplantation?

A registry analysis

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Abstract. The International Pancreas Transplant Registry data base was analyzed for the effect of HLA and mismatching on pancreas survival rate. Typing data was available for both donor and recipient at the A, B and DR loci in 524 of 855 cadaver cases reported since 1982 and in 37 related cases. For cadaver cases, the 1-year functional survival rates for grafts mismatched at ≤ 3 ($N=163$) versus ≥ 4 ($N=361$) A, B and DR antigens were 49% versus 39% ($P=0.121$); for technically successful (TS) cases the rates were 66% ($N=123$) versus 54% ($N=257$) ($P=0.038$). An effect was seen at A, B and DR loci, but the differences were not significant when considered separately. The analysis of TS related donor transplants showed a 1-year graft survival rate of 89% for HLA mismatched donors ($N=11$) and of 80% for HLA identical donors ($N=11$). The survival rate of the latter is significantly higher ($P=0.046$) than that of the TS cadaver donor transplants (59% at 1 year, $N=361$). The data suggest that the results of pancreas transplantation will be improved by minimizing HLA mismatches. However, a reanalysis with a more complete data base is needed before firm conclusions can be drawn.

Key words: Pancreas transplantation - HLA matching.

The major histocompatibility system (HLA in man) has several functions, including graft immunogenicity and host response, disease susceptibility, and cell cooperation in immune responses. The question of whether matching for HLA A, B and DR antigens improves kidney graft survival is at least as controversial since the introduction of new potent immunosuppressive drugs in transplantation as it was before.

A strong positive effect of HLA matching on outcome has been demonstrated in the Eurotransplant data [8] and also in Opelz's collaborative study [4] for renal transplantation. In pancreas transplantation, the question of HLA matching is compounded by the hypothetical possibility that the outcome might be worse in patients receiving a DR identical graft since the DR antigens are associated with susceptibility to diabetes [3].

We retrospectively analyzed the data reported to the International Pancreas Transplant Registry in order to answer the following question: is there an effect of A, B or DR matching or mismatching on pancreas graft outcome?

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Material and methods

Between 17 December 1966 and 26 April 1987, 1157 pancreas transplants in 1077 diabetic patients performed at 93 institutions were reported to the ACS/NIH Organ Transplant Registry and to the International Pancreas Transplant Registry [5]. Most of the cases have also been reported to the new International Registry (1100 transplants in 1022 patients). More than three-fourths of the transplants ($N=892$ or 77%) in the Registry have been performed since 1982. Because the results of pancreas transplantation have significantly improved with time and because DR typing has only been available in most institutions since 1982, the analysis of outcome according to HLA matching was only performed for the 892 cases reported to the Registry between 1 January 1983 and 26 April 1987.

Cadaver donors were the source of 855 pancreas transplants (792 primary, 53 secondary, 9 tertiary, and 1 quaternary). Living related donors were the source of 37 pancreas grafts (34 primary and 3 secondary). Kidneys were transplanted in 720 of the pancreas graft recipients (81%), 565 simultaneously with the pancreas and 155 before the pancreas transplant.

Cyclosporine A was given to 823 (92%) of the recipients. No data on blood transfusions or crossmatches were submitted to the Registry.

The information reported from the individual institutions on each case was entered into a Clinfo Computer System (VAX II/750, VMS Operating System, Digital Equipment Corp., Nashua, N.H.) to perform actuarial analyses of graft and patient survival rates. The significance of differences between various groups was calculated over the entire curves using the generalized Wilcoxon test, as modified by Gehan [2]. The results at 1 year are given in table form, but the curves in the figures are carried out beyond this point even though the number of cases observed was small.

The recipients were DR 3 in 25% of the cases, DR 4 in 34% of the cases, and both DR 3 and DR 4 in 31% of the cases; 90% of the recipients were DR 3 or DR 4 or both. The donors were DR 3 in 19% of the cases, DR 4 in 26% of the cases, and both DR 3 and DR 4 in 4% of the cases; 49% of the donors were DR 3 or DR 4 or both. This distribution of DR types in diabetic (recipients) and nondiabetic (donors) individuals is identical with that obtained in population studies [3].

For the purpose of analysis, all individual DR typing data from donors and recipients were introduced in a separate column. The same was done for the number of HLA-A, B and both HLA-DR matches and mismatches between pancreas donors and recipients. All split antigens were considered as nonshared antigens when not identical.

Grafts were counted as functioning only if and as long as the patients were reported to be insulin independent and normoglycemic. Technically successful (TS) grafts were those which did not fail for technical reasons. Technical failures were defined as loss of function within 3 days of transplant or graft loss at any time from local infection, primary thrombosis, bleeding, or other such complications necessitating graft removal.

For cadaver pancreas transplantation, data on HLA matching was available for analysis on 682 of 855 cases for the A and B loci (80%), 527 for the DR loci (62%), and 524 for all three loci (61%); the corresponding figures for 628 TS cases were 508 (81%), 383 (61%), and 380 (60%), respectively. In 15 cases (11 TS), the data on typing was received after the information had been entered into the computer for analysis.

Of the cases in which typing was reported to the Registry, more than one-third were mismatched for ≤ 2 A, B antigens, one-eighth for ≤ 1 DR antigen, and one-third for ≤ 3 antigens when all A, B, and DR loci were typed.

Results

Considering all cases (Table 1), the functional survival rates were not significantly higher for grafts mismatched for ≤ 3 than for ≥ 4 A, B and DR antigens (49% vs 39% at 1 year), for ≤ 2 than for ≥ 3 A and B antigens (52% vs 42%), and for 0 than for 1 or 2 DR antigens (54% vs 34% and 42%).

When all loci were considered, the grafts mismatched for ≥ 4 antigens had a significantly lower functional survival rate than those in which the HLA typing was not known (39% vs 47%, $P=0.012$). When only the A and B loci were considered, the functional survival rate for grafts mismatched for ≤ 2 antigens was significantly higher than that for grafts in which the HLA typing was not known (52% vs 35%, $P=0.043$).

These results suggest that minimizing the number of HLA mismatches has a beneficial effect on graft survival, and the analysis of functional survival rates of TS grafts according to the degree of HLA mismatching at all HLA loci supports this interpretation (Fig. 1).

The functional survival rate for TS grafts mismatched for ≤ 3 A, B and DR antigens (66% at one year) was significantly higher ($P=0.038$) than for grafts mismatched for ≥ 4 antigens (54% at 1 year),

Table 1. Cadaveric pancreas graft functional survival rates for all 1983-1987 cases according to number of HLA antigen mismatches between donor and recipient

No. of cases	No. of HLA mismatches (loci)	1-Year function	*P* values
	A, B and DR		
163	≤ 3	49%	≤ 3 vs $\geq 4 = 0.121$
361	≥ 4	39%	≤ 3 vs unknown = 0.199
317	Unknown	47%	≥ 4 vs unknown = 0.012[a]
	A, B		
258	≤ 2	52%	≤ 2 vs $\geq 3 = 0.052$
424	≥ 3	42%	≤ 2 vs unknown = 0.043[a]
159	Unknown	35%	≥ 3 vs unknown = 0.656
	DR		
62	0	54%	0 vs 1 = 0.066
260	1	32%	0 vs 2 = 0.313
205	2	42%	0 vs unknown = 0.583
313	Unknown	46%	1 vs 2 = 0.173
			1 vs unknown = 0.019[a]

[a] Statistically significant differences

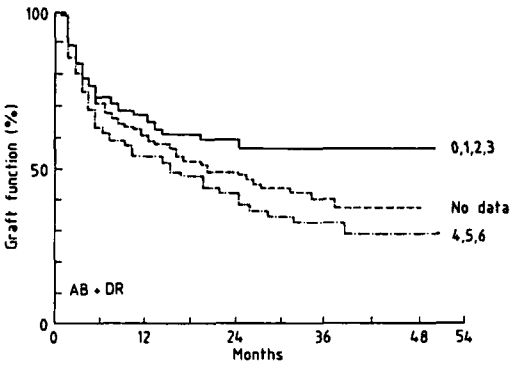

Fig. 1. Pancreas graft function by association with HLA AB and DR mismatches for all technically successful cadaver cases from 1 January 1983 to 26 April 1987

N	Legend	*N* FXN	12 MO FXN	*P* value
123	0, 1, 2, 3	80	66%	1 vs 2 = 0.038
257	4, 5, 6	130	54%	1 vs 3 = 0.433
248	No data	141	60%	2 vs 3 = 0.080

although neither of the groups in which the degree of mismatching was known was significantly different than the group in which it was unknown.

The beneficial effect of minimizing the number of HLA antigen mismatches is partly due to the A and B loci (Fig. 2) and partly to the DR locus (Fig. 3). The functional survival rate of TS grafts mismatched for ≤ 2 A, B antigens (67% at 1 year) was not significantly higher than that of grafts mismatched for ≥ 3 A, B antigens (58% at 1 year) but was significantly higher than that for the cases in which the degree of mismatching was unknown (45% at 1 year).

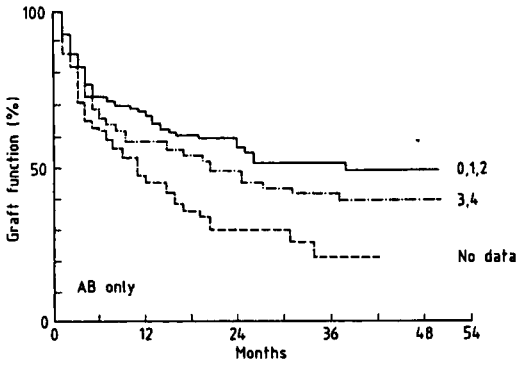

Fig. 2. Pancreas graft function by association with HLA AB mismatches for all technically successful cadaver cases from 1 January 1983 to 26 April 1987

N	Legend	*N* FXN	12 MO FXN	*P* value
201	0, 1, 2	127	67%	1 vs 2 = 0.058
307	3, 4	169	58%	1 vs 3 = 0.007
120	No data	55	45%	2 vs 3 = 0.279

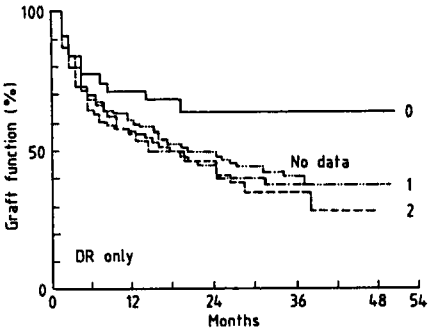

Fig. 3. Pancreas graft function by association with HLA DR mismatches for all technically successful cadaver cases from 1 January 1983 to 26 April 1987

N	Legend	*N* FXN	12 MO FXN	*P* value
47	0	33	72%	1 vs 2 = 0.098
183	1	96	58%	1 vs 3 = 0.110
153	2	83	56%	1 vs 4 = 0.247
244	No data	138	60%	2 vs 3 = 0.990
				2 vs 4 = 0.303
				3 vs 4 = 0.309

When the antigens of the DR loci were considered, the functional survival rate of TS grafts mismatched for zero antigen (72% at 1 year) was not significantly higher than those mismatched for 1 or 2 antigens (58% and 56% at 1 year).

A comparison of cadaver donor versus living related donor pancreas transplants (Fig. 4) showed that the functional survival rate was higher for TS grafts from HLA identical or mismatched donors than from cadaver donors (80% and 89% versus 59% at 1 year); however, only the HLA identical comparison was statistically significant (*P*-value calculated over entire curve and not just at 1 year).

Finally, no significant differences were seen when analyzing the data in the opposite way, that is, when considering matching rather than mismatching. Dividing the patients into subgroups according to the immunosuppressive treatment, technique of transplantation, and association with kidney transplants showed the same trends; the numbers of patients, however, were too small for statistical analysis.

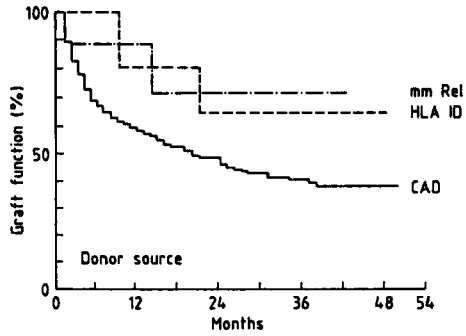

Fig. 4. Pancreas graft function by donor source for all technically successful cases from 1 January 1983 to 26 April 1987

N	Legend	*N* FXN	12 MO FXN	*P* value
639	Cadaver	361	59%	1 vs 2 = 0.159
11	mm REL	09	89%	1 vs 3 = 0.046
11	HLA-ID	08	80%	2 vs 3 = 0.902

Discussion

The Registry data suggest that HLA mismatching is, indeed, relevant in pancreas transplantation. Whether grafts mismatched for 1 A, B antigen would have a functional survival rate that is different from those mismatched for ≧2 A, B antigens will be the subject of a future analysis with a larger number of cases. DR data comparing ≦1 versus 2 DR mismatches will also be included in the analysis.

HLA typing information in the Registry is too incomplete to allow any firm conclusions to be drawn at present. (No information at all is available on 40% of the cases.) Moreover, the Registry includes at least 71 different typing institutions for which the quality of the tissue typing is not indicated in the Registry analysis. However, the distribution of antigens has been shown to be similar to that of diabetic and nondiabetic individuals in population studies [3]. Another factor is that the number of

cases at individual institutions is so small that the Registry provides the only means at this time for analysis of a possible effect of HLA matching.

Nevertheless, the graft survival rate in cases where the degree of HLA matching was unknown was intermediate between that of well-matched grafts and that of poorly matched grafts when all loci were considered. (This was not the case for the AB loci alone.) This uneven distribution highlights the need for a reanalysis when the data base is more complete.

It may well be that grafts which are matched for antigens predispose patients to a recurrence of diabetes [6]. If such is the case, one beneficial effect of minimizing the mismatches with regard to rejection would be offset. However, graft survival rates were, in fact, the highest in the best matched group. Since 90% of the recipients were DR 3 or DR 4 or both, it appears that recurrence of disease is not a major problem for cadaveric transplants from DR 3 or DR 4 donors [7]. This issue will be addressed more fully in future analyses.

Future analyses of HLA matching also need to consider the question of results when split antigens are considered as shared antigens, the effect of sharing antigens between the kidney and pancreas when the donors are different, and the effect of HLA matching or mismatching within the group in which rejection episodes are easily diagnosed (synchronous pancreas and kidney transplants from the same donor for all duct management approaches or all cases with urinary drainage), as well as in the group in which diagnosis of rejection episodes is difficult (duct injection or enteric drainage in the cases of pancreas transplant alone or pancreas transplants without a kidney from the same donor). With regard to this question of results under different conditions, a preliminary analysis suggests that minimizing the number of HLA mismatches has an additive effect with that of using approaches that facilitate the diagnosis of rejection in favorably influencing the functional survival rates of grafts [5].

The fact that solutions for prolonged pancreas preservation are now available [1, 9] means that efforts to prospectively minimize HLA mismatches with the donors in pancreas transplant recipients could begin.

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