HLA-B Matching Prolongs Allograft Survival in Islet Cell Transplantation

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Abstract

Islet cell transplantation (ITx) is an effective therapeutic approach for selected patients with type 1 diabetes with hypoglycemia unawareness and severe hypoglycemia events. In organ transplantation, human leukocyte antigen (HLA) mismatching between donor and recipient negatively impacts transplant outcomes. We aimed to determine whether HLA matching has an impact on islet allograft survival. Forty-eight patients were followed up after islet transplantation at our institution from 2000 to 2020 in a retrospective cohort. Patients underwent intrahepatic ITx or laparoscopic omental approach. Immunosuppression was dependent upon the protocol. We analyzed HLA data restricted to A, B, and DR loci on allograft survival using survival and subsequent multivariable analyses. Patients were aged 42.8 ± 8.4 years, and 64.3% were female. Diabetes duration was 28.6 ± 11.6 years. Patients matching all three HLA loci presented longer graft survival ($P = 0.030$). Patients with ≥ 1 HLA-B matching had longer graft survival compared with zero matching ($P = 0.025$). The number of HLA-B matching was positively associated with time of graft survival (Spearman's rho $= 0.590$; $P = 0.034$). Analyses adjusted for confounders showed that ≥ 1 matching for HLA-B decreased the risk of allograft failure ($P = 0.009$). Our data suggest that HLA-B matching between recipients and donors improved islet allograft survival. Matching all three HLA loci (A, B, and DR) was also associated with prolonged islet allograft survival. Prospective studies and a larger sample size are warranted to validate our findings.

Keywords

islet transplantation, type 1 diabetes, human leukocyte antigens, islet survival

Introduction

Islet cell transplantation (ITx) is an effective therapeutic approach for selected patients with type 1 diabetes affected by hypoglycemia unawareness and severe hypoglycemia events[1]. ITx may be considered among the safest of all transplantation procedures compared with solid organs[2], demonstrating improved glycemic control, decrease in the incidence of hypoglycemic events, and reduction of daily insulin dose, even in the absence of insulin independence, accompanied by improvement in quality of life[3–6]. Despite all the benefits reported, the prevention of islet rejection remains still a challenge in this field.

The human leukocyte antigen (HLA) system, which encodes the major histocompatibility complex, is known as an important factor for donor selection in solid organ transplantation[7]. For kidney transplant, the association between HLA matching and graft survival is well established[8–10]. On the other hand, the impact of HLA matching on pancreas transplant outcomes is still conflicting[11,12]. Most of the studies were limited by the small sample size or incomplete data

due to earlier eras of pancreas transplantation[13], but a positive role of HLA-B matching in preventing acute rejection in pancreas recipients has been shown[14]. The level of HLA mismatches correlates with the strength of the immune system response, and HLA typing is used to estimate the immunological risk of donor recognition[15].

Islet transplantation recipients often receive more than one islet infusion from different donors, and this procedure is responsible for an exposure of the recipients to multiple HLA

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Table 1. Chronic Immunosuppression Protocols in Clinical Islet Transplantation.

Period	Research protocol	Type of transplant	N	Induction	Immunosuppression maintenance
2000	NCT00315614	ITA + CD34⁺BMC	6	Daclizumab, etanercept	SIR, TAC
2001–2003	NCT00306098	ITA	16	Daclizumab, infliximab	SIR, TAC
2002–2004	NCT01309022 NCT00306098	ITA	5	Daclizumab	SIR, TAC
2005–2006	NCT00315627	ITA	3	Campath, etanercept	SIR, TAC
2005–2007	NCT00306098	ITA	4	Daclizumab, etanercept, exenatide	SIR, TAC
2005–2007	NCT00315614	ITA + CD34⁺BMC	3	Campath, etanercept	SIR, TAC
2008–2011	NCT00434811 NCT00464555	ITA (CIT)	8	ATG, etanercept	SIR, TAC
2015–2017	NCT02213003	ITA (omentum)	3	ATG, etanercept	TAC, MMF

ATG: rabbit anti-thymocyte globulin; BMC: bone marrow cell; CD34+BMC: CD34-enriched bone marrow cell; CIT: clinical islet transplantation consortium; ITA: islet transplant alone; MMF: mycophenolate mofetil; SIR: sirolimus; TAC: tacrolimus.

mismatches. The role of HLA matching on ITx outcomes has not been formally evaluated, and currently, HLA matching is not a criterion for islet donor selection. In this study, we aimed to evaluate the impact of HLA matching on graft survival in patients after ITx.

Materials and Methods

A retrospective cohort study was conducted on 48 patients with type 1 diabetes who underwent ITx at our institution between 2000 and 2020. Patients were followed-up for 6.4 ± 5.8 years. Forty-five patients underwent intrahepatic ITx and three patients received allogeneic islets via a surgical laparoscopic omental approach with islets distributed on the omentum surface. Induction and maintenance of immunosuppression were according to the clinical transplant protocol (Table 1). Protocol procedures were approved by the University of Miami Health Research Ethics Board. All patients provided informed consent and were enrolled in different research protocols (Table 1). Clinical, demographic, and transplant-related characteristics including the number of islet infusions, islet equivalents (IEQs) transplanted, glucagon-like peptide-1 (GLP-1) receptor agonist or dipeptidyl peptidase 4 inhibitor (DPP4i) use, and immunosuppressant drugs were recorded. HLA serological antigen typing was performed and matching calculations were based on the level of HLA-A, HLA-B, and HLA-DR antigen specificities.

We evaluated the impact of HLA donor and recipient matching on islet graft survival. Islet graft failure was defined as either a fasting C-peptide ≤0.10 ng/ml (in the absence of hypoglycemia) on two consecutive measurements obtained on different days or a stimulated C-peptide ≤0.3 ng/ml.

Statistical Analysis

Continuous variables with normal distribution were expressed as mean ± standard deviation. The Shapiro–Wilk test was used for normality assessment; asymmetrically distributed continuous variables were expressed as median and interquartile range (25th–75th); and categorical variables were expressed as absolute and relative frequencies. For between-group comparisons, Student's t-test was used for symmetrically distributed variables; Mann–Whitney U test for asymmetrically distributed variables; and Pearson chi-square or Fisher's exact test for categorical variables. Survival rates were estimated by Kaplan–Meier curves, while log-rank, Breslow, and Tarone-Ware tests were used to compare time with outcome (graft failure) between patients according to the number of HLA matching. Survival time was defined as the time from the first transplant to the date of graft failure. Patients lost to follow-up were censored either at outcome event or at the last recorded visit. Pearson and Spearman correlation tests were performed to identify correlation between number of matches or number of mismatches and time of graft survival. Multiple linear regression was used to identify a model that predicts the time of graft survival. Multivariable analysis was performed using the Cox proportional hazards model, considering graft failure as the dependent variable while the covariates were defined by either the clinical relevance or statistical significance. Values of $P < 0.05$ (two-tailed) were significant, and all data were analyzed on SPSS version 22.0 (SPSS Inc, Chicago, IL, USA).

Results

Patients were aged 42.8 ± 8.4 years, and 64.3% (n = 36) of the recipients were female. Mean body mass index of recipients was 23.6 ± 2.7 kg/m² and type 1 diabetes duration was 28.5 ± 11.6 years. First infusion of islet transplantation was done in 85.4% (n = 41) of the patients during the 2000 decade, while 14.6% (n = 7) occurred in the 2010 decade.

Induction immunosuppression consisted of anti-interleukin 2 (IL2) blockade with either daclizumab or basiliximab and anti-tumor necrosis factor (TNF) blockade with either infliximab or etanercept (Edmonton-like protocol) in 65% (n = 31) of patients of our cohort. Third-five percent (n = 17)
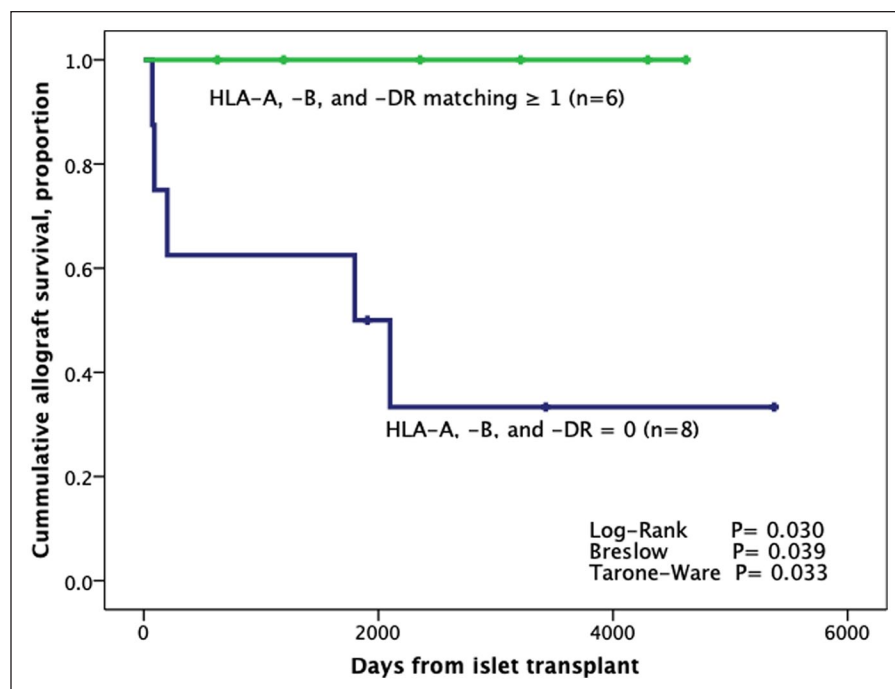
Figure 1. Kaplan–Meier analysis from the first transplant according to the combined (all three) HLA-A, HLA-B, and HLA-DR matching (n = 14). HLA: human leukocyte antigen.

of patients received T-cell depletion as immunosuppressive induction. Maintenance immunosuppression consisted of a dual combination strategy with sirolimus, tacrolimus, or mycophenolate mofetil (MMF). Autoantibodies glutamic acid decarboxylase (GAD) and islet antigen 2 (IA2) were present in 50% and 37.5% of the recipients, respectively. Only two patients developed donor-specific antibodies (DSA) anti-HLA while on immunosuppression, making unfeasible further analysis of this parameter.

Graft failure occurred in 18 patients (37.5%). Seven out of the 18 patients (38.9%) developed graft failure within the first year after transplant. HLA data analyzed were restricted to A, B, and DR loci. HLA-A matching was present in 28 out of the 48 patients (58%), HLA-B matching was present in 16 patients (33%), and HLA-DR matching was present in 27 patients (56%). HLA-DR3 or HLA-DR4 matching was present in 16 patients (33.3%), and it represents 60% of the HLA-DR matching patients. Thirty-four out of the 48 recipients were HLA-DR3 or HLA-DR4 (70.8%), while 3 (6%) of the donors were HLA-DR3, and 22 (45%) were HLA-DR4.

Islet graft survival in recipients with HLA-DR3 or HLA-DR4 alleles was not different from those recipients who were not HLA-DR3 or HLA-DR4 positive [$\chi^2 = 0.270$ ($df = 1$); $P = 0.870$].

We analyzed the impact of recipient and donor matching for HLA-A, HLA-B, and HLA-DR loci combined or independently, while data are reported as either 0 (for no matching) or ≥1 matching.

HLA-A, HLA-B, and HLA-DR Matching

Time of graft survival between patients who presented matching for all three HLA loci (HLA-A, HLA-B, and HLA-DR; n = 6) in comparison with patients with zero matching (n = 8) showed that patients with HLA-A, HLA-B, and HLA-DR combined matching have longer graft survival. ($P = 0.030$; Fig. 1).

HLA Matching for Specific Locus

Analyses of graft survival according to matching for specific locus showed that patients with no HLA-B matching (zero matching) developed graft failure at 9.6 ± 1.4 years compared with 15.2 ± 1.6 years in those who had ≥1 HLA-B matching (log-rank $P = 0.025$; Breslow $P = 0.054$; Tarone-Ware $P = 0.038$) (Fig. 2). Clinical and transplant characteristics of patients according to the presence of HLA-B matching are described in Table 2.

Univariate analyses were performed to identify possible confounders that could influence allograft survival independently of the HLA-B matching (Table 3). Recipient age, GLP-1 RA and/or DPP4i use, BMI, number of donors, IEQs infused, delta time between the first and second infusion, immunosuppression induction protocol, and GAD65/IA2 positivity were variables selected for this analysis. There was no statistical significance for any of the variables investigated. The Cox proportional-hazards model was performed to
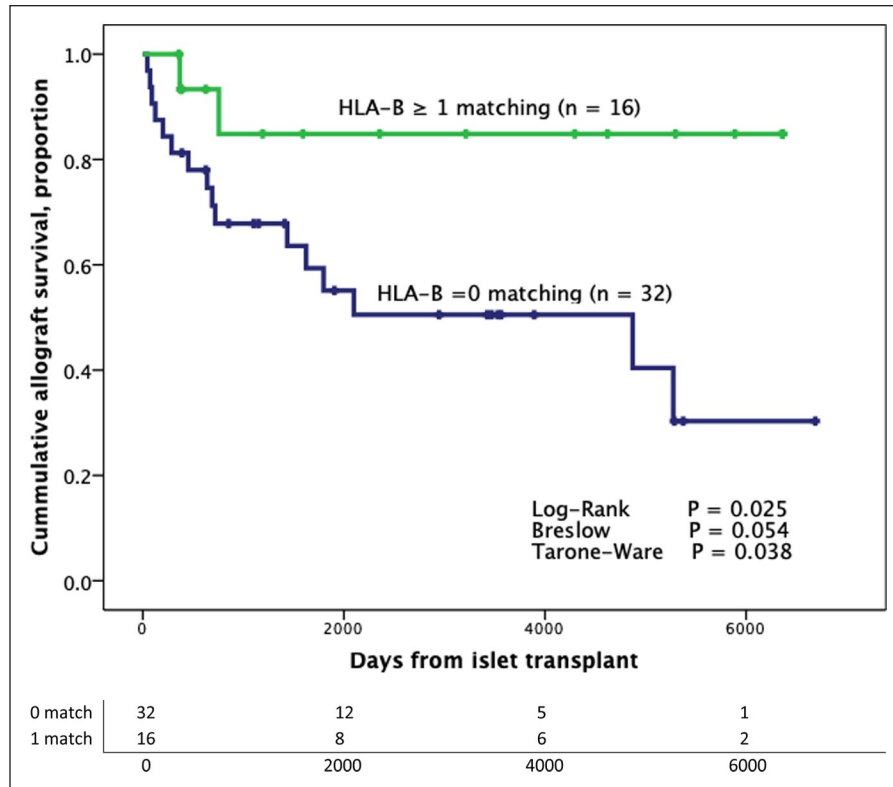
Figure 2. Kaplan–Meier analysis from the first transplant according to the presence of HLA-B. Patients were censored at the time of graft failure (n = 48). HLA: human leukocyte antigen.

Table 2. Clinical and Transplant Characteristics According to the Presence of HLA-B Matching.

	HLA-B	HLA-B	
	0 matching (n = 32)	≥1 matching (n = 16)	*P* value*
Female sex, n (%)	23 (71.9)	9 (56.2)	0.279
Age, years	44.8 ± 8.2	38.8 ± 7.6	*0.019*
BMI, kg/m²	23.3 ± 2.4	24.1 ± 3.1	0.339
Duration of diabetes	28.7 ± 10.8	26.0 ± 13.1	0.312
Number of donors	2 (1–3)	2 (1–3)	0.297
Infused islet per kg (1,000), IEQ	12.83 (8.1–16.5)	12.72 (9.6–15.4)	0.999
Δ Time (1st and 2nd infusion), months	5 (1–8)	1 (1)	*0.039*
Δ Time (1st and last infusion), months	20 (15–51)	33 (22–41)	0.686
Edmonton-like protocol immunosuppression induction, n (%)	17 (53.1)	14 (87.5)	*0.019*
T-cell depletion immunosuppression induction, n (%)	15 (46.9)	2 (12.5)	*0.019*
GLP1 RA and/or DPP4i use, n (%)	15 (46.9)	9 (56.2)	0.540
GAD65 autoantibodies, n (%)	11 (45.8)	9 (56.2)	0.519
IA2 autoantibodies, n (%)	9 (41.7)	6 (31.2)	0.505

Data are shown as mean and standard deviation, median and interquartile interval, or percentages. DPP4i: dipeptidyl peptidase 4 inhibitor; GAD65: glutamic acid decarboxylase 65-kilodalton isoform; GLP-1 RA: glucagon-like peptide-1 receptor agonist; HLA: human leukocyte antigen; IA2: islet antigen 2; IEQ: islet equivalent; BMI: body mass index.
*P value between groups and are according to χ^2 test, *T*-test, or Mann–Whitney *U* test as appropriate. Italicized values show a significant *P* value <0.05.

identify the best combined predictive effect, and variables were selected based on clinical relevance. The following were included in this model: immunosuppression induction protocol, GLP-1 RA use, number of donors, GAD65/IA2 positivity, and IEQs per kg infused. This analysis showed that ≥1 matching for HLA-B decreased the risk of graft failure compared with the zero matching group—hazard ratio (HR): 0.107; 95% confidence interval (CI): 0.022–0.508; *P* = 0.005.

Table 3. Univariate Analysis: OR (CI) and Significance Tests Considering Graft Failure as the Dependent Variable.

	Univariate OR (95% CI)	*P* value
Recipients age	1.026 (0.956–1.101)	0.478
GLP-1 RA use	1.000 (0.311–3.218)	0.999
Number of donors	0.912 (0.481–1.728)	0.777
T-cell depletion[a]	2.676 (0.711–10.0.72)	0.145
BMI	0.889 (0.715–1.131)	0.362
IEQ/kg infused	1.000 (1.0–1.0)	0.767
Δ Time (1st and 2nd infusion)	0.905 (0.757–1.082)	0.275
GAD 65/AI2 positivity	1.417 (0.374–5.365)	0.608

BMI, body mass index; CI, confidence interval; GAD65: glutamic acid decarboxylase 65-kilodalton isoform; GLP-1 RA: glucagon-like peptide-1 receptor agonist; DPP4i: dipeptidyl peptidase 4 inhibitor; IEQ/kg, islet equivalent per kilogram infused; OR, odds ratio.
[a]T-cell depletion as immunosuppression induction protocol.

Six out of the 32 patients (12.5%) with zero matching developed graft failure within 1 year after transplant. The impact of HLA-B matching on early (<1 year) versus late (≥1 year) graft failure was evaluated. There was no association between early graft failure and the absence of HLA-B matching ($P = 0.398$).

It was also observed that the number of HLA-B matching has a moderate positive correlation with time of graft survival (Spearman's rho = 0.590; $P = 0.034$).

Then, further analyses were performed, adjusting for confounders. A multiple linear regression model showed that the number of HLA-B matching predicts the time of allograft survival, adjusting for number of IEQ/kg infused and immunosuppression protocol [$F(3,9) = 8.041$, $P = 0.006$; $R^2 = 0.728$).

HLA-B mismatch, on the other hand, presented a number ranging from 0 to 7 and, as expected, is positively correlated with the number of donors (Spearman's rho = 0.925; $P < 0.0001$). The number of HLA-B mismatch was negatively correlated with time of graft survival (Spearman's rho = −0.775; $P < 0.0001$) in patients who presented allograft failure (n = 18).

A subanalysis of the patients who received islets from a single donor was performed (n = 18), resulting in 22.2% (n = 4) of the patients matching for HLA-B, while 77.8% had zero matching (n = 14). Fig. 3 shows the analysis of the time of graft survival according to HLA-B matching in this subgroup of patients.

No significant findings were observed in the analyses of time of graft survival for locus-specific HLA-A matching (log-rank $P = 0.965$) or HLA-DR matching (log-rank $P = 0.955$). HLA-A, HLA-B, and HLA-DR loci combinations were also evaluated (HLA-A and HLA-B; HLA-A and HLA-DR; HLA-B and HLA-DR). There were no significant differences in graft survival for any locus combination between recipients and donors (data not shown).

Discussion

In this study, we aimed to determine whether HLA matching has any impact on graft survival in patients who received islet transplant. HLA-B matching showed an association with islet graft survival and conferred protection for allograft failure, after adjustment for immunosuppression induction protocol, GLP-1 RA use, number of donors, GAD65/IA2 positivity, and number of IEQ/kg infused. In this same context, patients who matched for all three HLA loci (A, B, and DR) also presented a longer graft survival.

Human HLA genes are located on chromosome 6 and encode for three major class I alleles (HLA-A, HLA-B, and HLA-C) and three major class II alleles (HLA-DR, HLA-DQ, and HLA-DP). The contribution of the HLA genotype on genetic risk for T1D is well determined[16].

The highest risk HLA-DR3/DR4 DQ8 genotype has been shown to be highly associated with beta-cell autoimmunity. Indeed, the study-specific estimates for the association between the HLA class II DR3/DR4 genotype and type 1 diabetes showed a general odds ratio of approximately 16, demonstrating the importance of this genetic region for T1D[17]. However, these genes cannot completely explain the association between type 1 diabetes and the MHC region. In experimental models, MHC class I–mediated events, principally involving *HLA-B*39*, contributed to the etiology of type 1 diabetes[18].

The effect of HLA compatibility on solid organ transplantation outcomes has been the focus of several studies spanning more than a decade, but there is no conclusive evidence of this effect in the ITx field[19]. In 2009, Vantyghem et al followed up a small cohort of 14 patients who received ITx (two to three infusions) for up to 39 months after transplant. In this study, there were no significant differences in the number of HLA mismatches in patients with optimal versus suboptimal primary graft function[20]. Studies that analyzed the role of HLA matching on pancreas transplantation outcomes reported controversial results. Rudolph et al studied 1,219 pancreas transplants performed at the University of Minnesota and observed a correlation between the number of HLA-A, HLA-B, HLA-C, HLA-DR, and HLA-DQ mismatches and acute rejection. However, HLA matching did not affect patient or graft survival rates[14]. Similarly, Lo et al analyzed the significance of HLA matching on the outcome of simultaneous pancreas-kidney transplantation in a cohort of 297 patients and found that the degree of HLA mismatching was associated with an increased risk for acute rejection at 1 year, but did not affect short-term patient or graft survival rates[21]. In this same context, Berney et al found a 2.6 times higher relative risk of acute rejection among patients with multiple HLA mismatches, although without evidence that HLA matching was associated with improved kidney or pancreas survival[12]. Other authors reported that pancreas after kidney and pancreas transplant alone recipients had better outcomes if the donor and recipient shared at least one
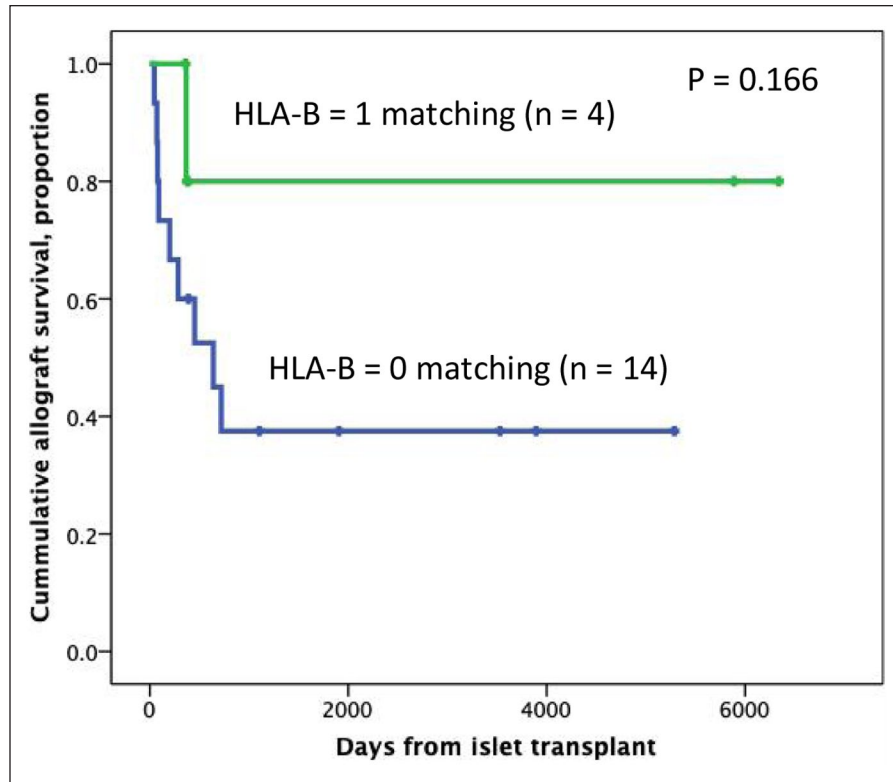
Figure 3. Kaplan–Meier analysis from the first transplant according to the presence of HLA-B. Subgroup analysis considering patients who received from a single donor. Patients were censored at the time of graft failure (n = 18). HLA: human leukocyte antigen.

matching on the HLA-A and/or HLA-B loci[11]. On the other hand, Mittal et al reported that neither degree of HLA mismatch (0–4 vs 5–6) nor DR mismatch (0, 1, or 2) was associated with pancreas graft failure in a cohort of 433 pancreas transplant recipients[22].

In our study, two patients developed donor-specific antibodies and we did not perform analyses considering this parameter. A previous study observed that pretransplant DSAs and de novo development of post-transplant DSAs were not associated with reduced graft survival and reduced graft function[23].

Our results seem to be in accordance with the proposed interactive effect of the HLA class I and the HLA class II regions on the regulation of the immune response[24]. In our study, matching for HLA-B is associated with prolonged graft survival. Therefore, the number of B matching predicts the time of graft survival, after adjustment for IEQ/kg infused, GLP-1 RA use, number of donors, GAD65/IA2 positivity, and immunosuppressive induction protocol. These covariates are listed as important factors for favorable outcomes in islet transplantation[25]. In the subset analysis of the time of graft survival in patients who received islets from a single donor, only 4 patients had ≥1 HLA-B matching and 14 had no HLA-B matching ($P = 0.166$). This analysis is not statistically significant probably due to the small sample size.

In our study, patients who had ≥1 HLA-B matching also received the second infusion in a shorter time interval in comparison with patients with zero HLA-B matching. However, there was no association between delta time of infusions and graft survival. This parameter was previously analyzed by Forbes et al who showed that shorter time interval between islet transplants was significantly associated with greater insulin dose reduction, but not associated with graft survival or any other metabolic measurement[26].

Polymorphisms of class I *HLA-B* gene are associated with T1D and are considered one of the major genetic determinants of T1D likewise polymorphisms of class II HLA genes encoding DQ, DR, and, less frequently, DP[17]. The most significantly protective T1D-associated class I allele is B*57:01[27]. The observed HLA-B association may also be explained by the strong linkage disequilibrium in the HLA region with nearby causal gene(s) in some populations[28]. Historically, a greater impact of HLA-A, HLA-B, and HLA-DR antigens has been observed in renal graft rejection[29], with a larger effect for B and DR matching[30]. More recently, a meta-analysis evaluated HLA-A, HLA-B, and HLA-DR mismatches and graft failure in renal transplantation; after adjustment, each incremental increase of HLA-DR mismatch was significantly associated with 12% higher risk of overall graft failure (HR: 1.12; 95% CI: 1.05–1.21; $P = 0.002$)[31].

Another study in renal transplantation analyzed 106,019 recipients from the Scientific Registry of Transplant Recipients database and observed that HLA-B and HLA-DR mismatches were all significantly associated with worse graft survival outcomes[32].

Taking into account the role of class I and class II region in the immunological system and the previous studies reporting an association between HLA matching with graft outcomes, we believe that the evaluation for HLA matching should be considered an important factor for donor eligibility in islet transplantation.

Hopefully, in the near future, the careful selection of stem cell islet donors, aiming at HLA matching with the recipient, will be a reality.

The results of this study, however, carry limitations associated with the retrospective design, the small sample size, and the restriction of HLA matching to A, B, and DR loci, but not DQ locus.

Our data suggest that patients who presented matching for HLA-B showed improved islet allograft survival. Also, matching all three HLA loci (A, B, and DR) also conferred longer islet allograft survival when compared with zero matching, suggesting that HLA matching assessment should be considered for islet transplantation. To validate our findings, the analysis of HLA matching in islet transplantation is worth assessing in prospective studies on a larger number of patients.

Authors' Contributions

Joana R N Lemos, David A Baidal, Raffaella Poggioli, Virginia Fuenmayor, and Rodolfo Alejandro participated in the writing of the manuscript. Joana R N Lemos participated in data analysis. Joana R N Lemos, Virginia Fuenmayor, Carmen Chavez, and Ana Alvarez participated in data collection. David A Baidal, Camillo Ricordi, and Rodolfo Alejandro participated in the research design.

Availability of Data and Materials

The data that support the findings of this study are available on request from the corresponding author Rodolfo Alejandro.

Ethical Approval

Protocol procedures were approved by the University of Miami Health Research Ethics Board.

Statement of Human and Animal Rights

This article does not contain any studies with human or animal subjects.

Statement of Informed Consent

All patients provided informed consent and were enrolled in different research protocols.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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