Published in final edited form as:

Cell Transplant. 2012 ; 21(5): 901–908. doi:10.3727/096368911X612468.

HLA Class I Sensitization in Islet Transplant Recipients – Report from the Collaborative Islet Transplant Registry

Bashoo Naziruddin^{1,*}, Steve Wease², Donald Stablein², Franca B. Barton², Thierry Berney³, Michael R. Rickels⁴, Rodolfo Alejandro⁵, and The CITR Investigators⁶

¹Baylor Regional Transplant Institute, Dallas, TX, 75246, USA ²The EMMES Corporation, Rockville, MD, 20850, USA ³Service of Transplantation and Visceral Surgery, Geneva University Hospital and Medical School, Geneva, 1211, Switzerland ⁴Institute for Diabetes, Obesity and Metabolism, University of Pennsylvania School of Medicine, Philadelphia, PA, 1904, USA ⁵The Diabetes Research Institute, University of Miami Leonard M. Miller School of Medicine, Miami, FL, 33021, USA

Abstract

Pancreatic islet transplantation is a promising treatment option for patients severely affected with type 1 diabetes. This report from CITR presents pre- and post-transplant human leukocyte antigen (HLA) class I sensitization rates in islet alone transplantation. Data came from 303 recipients transplanted with islet alone between January 1999 and December 2008. HLA class I sensitization was determined by the presence of anti-HLA class I antibodies. Panel-reactive antibodies (PRA) from prior to islet infusion and at 6 months, and yearly post-transplant was correlated to measures of islet graft failure. The cumulative number of mismatched HLA alleles increased with each additional islet infusion from a median of 3 for one infusion to 9 for three infusions. Pre-transplant PRA was not predictive of islet graft failure. However, development of PRA 20% post-transplant was associated with 3.6 fold ($p=.001$) increased hazard ratio for graft failure. Patients with complete graft loss who had discontinued immunosuppression had significantly higher rate of PRA 20% compared to those with functioning grafts who remained on immunosuppression. Exposure to repeat HLA class I mismatch at second or third islet infusions resulted in less frequent development of de novo HLA class I antibodies when compared to increased class I mismatch. The development of HLA class I antibodies while on immunosuppression is associated with subsequent islet graft failure. The risk of sensitization may be reduced by minimizing the number of islet donors used per recipient, and in the absence of donor-specific anti-HLA antibodies, repeating HLA class I mismatches with subsequent islet infusions.

* Address Correspondence to: Bashoo Naziruddin, Ph.D., Islet Cell Laboratory, Transplant Services, Baylor University Medical Center, 3410 Worth Street, Dallas, TX 75246, Phone: (214) 820-2662; Fax: (214) 820-7142, bashoon@baylorhealth.edu.

⁶See acknowledgement

All authors had no conflicts of interest on this study.

The Collaborative Islet Transplant Registry is funded by a grant from the National Institute of Diabetes, Digestive and Kidney Diseases, National Institute of Health, USA and by a supplemental grant from the Juvenile Diabetes Research Foundation International. Additional data are made available through cooperative agreements with the US United Network for Organ Sharing and the Administrative and Bioinformatics Coordinating Center of the City of Hope. The CITR Investigators contributing data to this report are listed in Appendix I.

Keywords

Islet Transplantation; HLA Sensitization; HLA Class I; Panel Reactive Antibodies

Introduction

Pancreatic islet transplantation is an emerging β -cell replacement approach to achieve insulin independence or improve glycemic control for patients with “brittle” type 1 diabetes (T1D). While insulin independent rates have been ~60% at one year, islet graft function decreases over time with insulin independence rates declining to ~13% at five years (1,8,10,22,26). Many factors could contribute to either early or late loss of islet graft function, including post-transplant inflammation (13), potential toxicity of immunosuppressive drugs (24), recurrence of autoimmunity (25,28), beta cell exhaustion (19,27), and alloimmune rejection. Several reports (4–7,9,15,16,18,20,21) have shown the development of alloimmune responses in islet transplant recipients with detection of antibodies against islet donor human leukocyte antigen (HLA) class I and II molecules. HLA sensitization can be explained by the absence of HLA matching at the time of selection of donor pancreas and the use of multiple islet infusions to achieve a sufficient engrafted islet mass to support insulin independence, practices that may expose an islet recipient to a number of mismatched HLA alleles.

The effect of HLA sensitization on islet graft function is not sufficiently clear (6). The presence of anti-HLA antibodies pre-transplant has been associated with worse islet graft functional outcomes in some (4,16), but not all (7), studies; however, the negative report did not determine donor specificity of the detected alloantibodies. The development of de novo anti-HLA antibodies post-transplant has also been associated with islet graft failure (15,18,20), although some islet transplant recipients who develop a positive panel-reactive antibodies (PRA) may continue to have well functioning islet grafts (2,7). Regardless of the mechanism of islet graft deterioration, patients who discontinue immunosuppressive drugs following complete or partial islet graft loss seem to be at high risk for HLA sensitization (5,7,9,21).

The Collaborative Islet Transplant Registry (CITR) contains data on islet transplantation contributed from twenty eight North American medical institutions, three European and two Australian centers between January 1999 and December 2008. As of April 2009, the registry contained data from 412 islet transplant recipients of 828 infusions derived from 905 donor organs (26). This report describes the analysis of HLA class I sensitization among 303 islet alone transplant recipients. The role of multiple islet infusions, the number of HLA mismatches and immunosuppression withdrawal on the development of HLA class I sensitization were analyzed, as well as the effect of HLA sensitization on islet graft failure. Currently the data on HLA class II PRA is incomplete. Efforts are being made to complete data collection on sensitization to HLA class II and a comprehensive analysis will be the focus of future reports.

Patients and Methods

Islet transplant centers contributing to the CITR obtained local IRB approval and written informed consent from all patients whose data were entered. The data are rigorously monitored to comply with Code of Federal Regulations (CFR) requirements. This study reports an analysis of data collected from 303 recipients transplanted with islets alone between January 1999 and December 2008. Patients receiving allogeneic islet alone transplants generally are required to have had type 1 diabetes mellitus for more than 5 years, be between 18–65 years of age, and have extreme difficulties with glycemic control indicated by either hypoglycemia unawareness with episodes of severe hypoglycemia, or marked glycemic lability with consistently elevated HbA1c levels (1,26). Information on donor HLA phenotyping was collected from the United Network for Organ Sharing (UNOS) for North American patients, and data on all recipients was provided by the transplant centers.

Panel Reactive Antibodies (PRA)

HLA sensitization in islet transplant patients is reported as percent PRA against class I HLA. PRA was measured either by the complement-dependent cytotoxicity assay using a reference panel consisting of lymphocytes with known HLA specificity, enzyme-linked immunosorbent assay (ELISA) using antigen coated trays, FLOW PRA which is based on antigen coated fluorescent beads, and/or Luminex solid phase assays (11). PRA provides the percent of cells that were either killed by patient's serum or the percent of cells that showed binding of immunoglobulins to HLA proteins. We analyzed positive PRAs in this study as either 1 – 19% or 20%.

Statistical Analysis

Descriptive statistics are presented as numbers for qualitative variables and mean $\pm$ SD or median with range for quantitative variables. Boxplots are used to summarize data. The “star” in the boxplot represents the mean value while the lower, middle, and upper lines of the box represent the 25th, 50th, and 75th percentile respectively. The square roots of pre-transplant and 2 year post transplant PRA were plotted. McNemar's test was used to determine if islet transplantation was associated with developing a post transplant PRA 20%. Univariate analysis was performed using chi-square test to compare number of PRA 20% patients with pre transplant PRA, number of islet infusions, and with re-exposure to HLA class I mismatches. Proportional hazards analysis of time to graft failure was performed with fixed and time-varying covariates. A *p*-value of <0.05 was considered statistically significant. All analyses were performed in SAS 9.2 for Windows (SAS Institute Inc., Cary, NC).

Results

The number of patients analyzed was 303 from 27 centers; 81 patients received one, 144 patients received two, and 78 patients received three or more infusions. The mean age of the recipients was 44 $\pm$ 9.7 years and included 108 males and 195 females (Table 1). Fourteen out of 303 patients had a pre-transplant PRA 20% and 37/303 patients had low levels (1–19%)

of PRA. The registry does not have alloantibody specificity data, and so cannot determine whether unacceptable antigens were avoided and/or if prospective cross-matches were negative before proceeding with the islet transplantation in these 51 PRA positive patients.

The median number of class I (A and B) mismatches at first islet infusion was 3 with a range of 0 to 8. A mismatch of 5 to 8 class I antigens reflects infusion of combined islet preparations from two donor pancreata. The median number of mismatches increased to 6 (range 2–12) for the second infusion and 9.5 (range 6–15) for the third infusion (Table 2). Results were similar for the number of class II (DR and DQ) mismatches. The median number of mismatches for the combination of all HLA alleles reported (A, B, DR, DQ) are 5 for one infusion, 11 for two infusions and 17 for three infusions (Table 2).

The prevalence of a class I PRA $\geq 20\%$ before and after one (A) or two (B) or three (C) islet infusions is shown in Figure 1. The follow up period was 6 months and yearly after 1 year for up to 3 years. At first infusion 289 patients were $<20\%$ for class I PRA. During the follow up period after a single islet infusion, 4/102 at 6 months, 4/70 at one year, 4/42 at two year and 4/25 at third year had a PRA $\geq 20\%$. At the time of a second islet infusion 4/197 patients were PRA $\geq 20\%$, and subsequently 2/123 were $\geq 20\%$ at 6 month, 6/109 at 1 year, 9/81 at 2 years, and 8/58 at 3 years. Similarly 1/69 patients who received a third islet infusion was $\geq 20\%$ for class I PRA at the time of infusion, and then 1/40 were $\geq 20\%$ at 6 months, 0/38 at 1 year, 0/28 at 2 years and 4/23 at 3 years.

Figure 2 shows the development of class I PRA ($\geq 20\%$) at two years post-final infusion when compared to the pre-transplant status after one or two or three islet infusions in 161 patients under immunosuppression. Of 152 patients with pre-transplant class I PRA $<20\%$ (Q1 and Q3) and assayed at 2 years post final islet infusion, 15 (9.9%) developed a PRA $\geq 20\%$. The increase was significant ($p<.001$) and the one case showing $\geq 20\%$ PRA during pre-transplant period (Q3) was determined to have resolved with a decrease in PRA to 0%. After two islet infusions the increase in number of patients with $\geq 20\%$ PRA (13/83) was more when compared to one infusion (2/42). Surprisingly among 27 patients with three infusions, there was no evidence of increase in PRA.

The cumulative incidence of class I PRA $\geq 20\%$ among 250 islet transplant patients under immunosuppression is shown in Figure 3. At one year post-first infusion 3% of patients developed a class I PRA $\geq 20\%$ and the incidence increased to 9% at 2 years, 13% at 3 years, 26% at 5 years, and 33% at 6 years. As shown in Figure 4, median PRA among patients with functioning islet grafts was zero for all the four follow up periods; however, 4/180 patients at 6 months, 4/152 at 1 year, 6/102 at 2 years, and 5/75 at 3 years had a class I PRA $> 20\%$. Among patients with complete graft loss median PRA was 5% at 6 months, 0% at 1 year, 4.5% at 2 years, and 25% at 3 years post-transplant. In an analysis of PRA as a predictor of time to initial graft failure, elevated baseline PRA was not a risk factor as failure rates were 100/252 (39.7%), 20/37 (54.1%) and 3/14 (21.4%) for those with % PRA 0, 1–19 and ≥ 20 , respectively. Among those with % PRA 0–19 at baseline, recent elevation of PRA $\geq 20\%$ during follow-up was a risk factor for graft failure (HR=3.6 $p=.0014$).

We analyzed development of post-transplant PRA $\geq 20\%$ by baseline and treatment characteristics (Table 3). Among 217 patients with 0% PRA before islet transplant, 13% (28/217) developed $\geq 20\%$ PRA, whereas 38% of patients with 1–19% PRA at baseline showed development of $\geq 20\%$ PRA. This data showed that presence low levels PRA at first infusion will significantly increase ($p < 0.001$) the possibility of development class I PRA to $\geq 20\%$. However multiple islet infusions did not increase the possibility of development of class I PRA of $\geq 20\%$ significantly when compared to single infusion (15% vs. 20%; $p = 0.26$). HLA class I sensitization ($\geq 20\%$ PRA) among patients reexposed to repeat HLA donor mismatches (8%; $n = 39$) was less than those patients who were not reexposed (20%; $n = 35$). However, this difference did not reach statistical significance ($p = 0.12$) as shown in Table 3.

Discussion

This report of CITR data represents the largest analysis to date of HLA class I sensitization in islet transplant recipients. The results show that i) multiple islet infusions increased the number of HLA mismatches to which transplant recipients were exposed; ii) multiple islet infusions did not further increase the risk of sensitization over a single islet infusion; iii) the proportion of patients developing anti-HLA class I antibodies increased over time even in the presence of immunosuppression; and iv) the development of a post-transplant PRA $\geq 20\%$ was associated with subsequent islet graft failure. The limited pool of donor organs precludes efficient islet transplant allocation according to HLA matching. Hence it is expected that multiple infusions will expose recipients to increased numbers of HLA mismatches. Our results confirm this expected outcome as the majority of islet recipients who received two islet infusions were exposed to at least six HLA class I mismatches. Data from the Edmonton group (4,5) showed that the median number of class I mismatches was 3 with a range of 0–7, and for both class I and II the number of mismatches in their patient population ranged from 1 to 19 with a median of 8.5; however, there was no relationship between the number of mismatches and the development of HLA antibodies. Development of approaches that can achieve insulin independence after single islet transplantation will minimize patient's exposure to HLA mismatches which in turn may decrease the risk for allosensitization.

Another important issue for the transplantation of islets mismatched for HLA is the effect of pre-transplant sensitization on subsequent islet graft function and survival. The inadvertent transplantation of islets to recipients pre-sensitized against donor-specific HLA can result in rapid islet graft loss (16), and the presence of a pre-transplant class I PRA $> 15\%$ was associated with islet graft failure that was largely explained by the presence of islet donor-specific antibodies (4). In the present report, we did not find a significant relationship between a positive PRA pre-transplant and subsequent islet graft failure, however, donor specificity data was not available. Most centers now perform prospective cross-matches, and in the cases of positive PRA pre-transplant, avoid unacceptable antigens by excluding donors with the same specificities as anti-HLA antibodies regardless of the cross-match (21).

De novo HLA sensitization may also be one of the factors that are associated with loss of islet graft function. The adverse effect of HLA sensitization in recipients of kidney (12,14), heart (3) and lung (23) transplants has been reported earlier. Among pancreas transplant recipients (simultaneous pancreas kidney), 21% developed anti-HLA antibodies (6), and the presence of anti-HLA antibodies correlated with poor pancreas graft survival. Islet grafts may be more “sensitive” to humoral immunity when compared to solid organ grafts and may be more rapidly destroyed in the presence of alloantibody (17). In the first report associating islet graft loss with sensitization to mismatched donor HLAs (18), patients who developed anti-HLA antibodies had significantly impaired islet graft function when compared to non-sensitized patients. Subsequent reports have also demonstrated a temporal relationship with the development of islet donor specific anti-HLA antibodies and subsequent islet graft functional deterioration and failure (15,20), although there have also been cases reported where the development of donor specific anti-HLA antibodies was not related to any deterioration in islet graft function (2) or long-term survival (7). Nonetheless, based on results from a larger pool of patients, Campbell et al (5) have reported that 26 out of a total of 98 (27%) islet transplant patients developed *de novo* donor specific anti-HLA antibodies while on maintenance immunosuppression that was associated with significantly worse islet graft function when compared to the patients without sensitization. The data reported here extend these findings by demonstrating a significantly increased risk for islet graft failure following the development of a PRA ≥ 20% post-transplant.

Our data also confirm earlier reports (5,7,9,21) of increased HLA sensitization among patients with failed islet grafts who discontinued their immunosuppression. Development of HLA sensitization among these patients remains a concern because of the potentially prolonged waiting time for subsequent organ transplants (e.g. pancreas or kidney), if needed. A final consideration is that the type of immunosuppression may have a major effect on anti-HLA antibody production. While the Edmonton group showed that 27% of patients treated with glucocorticoid free immunosuppression develop *de novo* anti-HLA antibodies (5), the Geneva group (9) demonstrated that 0/27 patients receiving low-dose glucocorticoids as part of their immunosuppression for previous or simultaneous kidney transplants developed *de novo* anti-HLA antibodies, whereas 2/8 patients receiving Edmonton immunosuppression and 2/3 patients during withdrawal of immunosuppression became sensitized. These results suggest that glucocorticoid-free immunosuppression may not sufficiently control the development of alloimmune response to transplanted islets.

In summary, the present report demonstrates that the development of anti-HLA class I antibodies post-transplant represents a significant risk for subsequent islet graft failure.

Acknowledgments

Expert comments by Dr. T. Mohanakumar, Washington University in St. Louis are gratefully acknowledged.

The following institutions and individuals contributed to the reporting and/or analysis of the data included in this manuscript.

Baylor College of Medicine/The Methodist Hospital (Houston, TX, USA). PI: John A. Goss; Cheryl Durkop; Tiffany Zgabay

Baylor Regional Transplant Institute (Dallas, TX, USA). PI: Marlon Levy; Darrell Grimes; Bashoo Naziruddin; Kerry Purcell; Shinichi Matsumoto, Morihito Takita

Benaroya Research Institute (Seattle, WA, USA). PI: Carla Greenbaum; Marli McCulloch-Olson; Marilyn Reeve

The Carolinas Medical Center (Charlotte, NC, USA). PI: Paul Gores; Melissa McGraw

The Columbia University (New York, NY, USA). PI: Mark A. Hardy; Joan Kelly; Zhuoru Liu

Emory Transplant Center (Atlanta, GA, USA). PI: Mark Rigby; Elizabeth Holbrook; Marti Sears; Jenny Joseph

Geneva/GRAGIL Network (Geneva, Switzerland). PI: Thierry Berney; Elsa Boely; Coralie Brault; Sandrine Demuylder-Mischler; Laure Nasse

Lille University Hospital (Lille Cedex, France). PI: Francois Pattou; Rimed Ezzouaoui; Valery Gmyr; Julie Kerr-Conte; Violeta Raverdy; Marie Christine Vantghem

Harvard Medical School (Boston, MA, USA). PI: Enrico Cagliero; Arthur Dea; A. Kadir Omer; Heather Turgeon; Gordon Weir

The Mayo Clinic (Rochester, Minnesota, USA). PI: Yogish Kudva; Jarrett Anderson; LeAnn Batterson; Deborah Dicke-Henslin; Jane Fasbender Michelle Kreps

NIH Clinical Transplant Center (*Bethesda, Maryland, USA*). PI: David Harlan; Eric Liu; Pat Swanson

Northwestern University (Chicago, IL, USA). PI: Dixon Kaufman; Elyse Stuart; Patrice Al-Saden

San Raffaele Institute (Milan, Italy). PI: Antonio Secch; Marina Scavini; Paola Maffi; Paola Magistretti

Southern California Islet Consortium (SCIC) (Duarte, CA, USA). PI: Fouad Kandeel; Jeanette Hacker; Lisa Johnson; Jeffrey Longmate; KD Shiang; Keiko Omori; Aria Miller

St. Vincent's Institute (Fitzroy, Victoria, Australia) PI: Tom Kay; Lina Mariana; Kathy Howe

Swedish Medical Center (Seattle, WA, USA). PI: William Marks; Terri Baker

Toronto General Hospital (Toronto, Ontario, Canada). PI: Mark Cattral; Gary Levy; Lesley Adcock; Dianne Donat; Jill Sheedy; Elizabeth Wright; Meerna Nsouli; Mark Haslegrave

The University of Alabama (Birmingham, Alabama, USA). PI: Juan Luis Contreras; Deborah Seale; Patricia Wilson

The University of Alberta Edmonton (Alberta, Canada). PI: A. M. James Shapiro; Co-PI: Peter Senior; Parastoo Dinyari; Janet Wright; Tatsua Kin

The University of California, San Francisco (San Francisco, CA, USA). PI: Peter Stock; Co-PI: Andrew Posselt; Joan McElroy; Greg Szot; Debbie Ramos; Tara Rojas; Kristina Johnson; Mehdi Tavakol

The University of Chicago (Chicago, IL, USA). PI: Piotr Witkowski; Matthew Connors; Mark Lockwood; Kathleen Singraber

The University of Colorado Health Sciences Center (Auora, CO, USA). PI: Alexander Wiseman; Betsy Britz; Ron Gill; Heather Sours; Antony Valentine; usan George; Meyer Belzer

The University of Illinois, Chicago (Chicago, IL, USA). PI: Jose Oberholzer; Co-PI: Enrico Benedetti; Co-PI: James Bui; Co-PI: Charles Owens; Michael Hansen; Bruce Kaplan; Joan Martellotto; Travis Romagnoli; Barbara Barbaro

The University of Miami (Miami, FL, USA). PI: Rodolfo Alejandro; Co-PI: Camillo Ricordi; David Baidal; Pablo Cure; Tatiana Froud; Maricruz Silva-Ramos

The University of Minnesota (Minneapolis, MN, USA). PI: Bernhard J. Hering; Barb Bland; Kathy Robin Jevne; David Radosevich; Anne Nettles; Sandra White; A.N. Balamurugan

The University of Massachusetts Medical Center. (Worcester, MA, USA) PI: Aldo Rossini; Celia Hartigan; Michael Thompson

The University of Pennsylvania (Philadelphia, PA, USA). PI: Ali Naji; Co-PI: Michael Rickels; Eileen M. Markmann; Diane McLaughlin; Maral Palanjian

The University of Tennessee, Memphis (Memphis, TN, USA). PI: A. Osama Gaber; Barbara Culbreath

The University of Virginia (Charlottesville, VA, USA). PI: Kenneth Brayman; John Angle; Donna Broshek; Jason Freeman; Klaus Hagspiel; Boris Kovatchev; Anthony McCall; Claire McKinley; Robert Sawyer; Julie Straub; Timothy Schmitt;

The University of Wisconsin (Madison, WI, USA). PI: Jon Odorico; Nancy Radke

Washington University, St. Louis (St. Louis, MO, USA). PI: Niraj Desai; Heather Robertson

Westmead Hospital (Wentworthville, NSW, Australia). PI: Philip Oconnel; Patricia Anderson; Lindy Williams

Coordinating Center: The EMMES Corporation (Rockville, MD, USA). PI: Franca B. Barton; Co-PI: Don Stablein; Yamini Damodharan; Christina Mandzuk; Andrew Heitman; James Cravens; Bryan Calaway; Jess Long; Chuck Wagner, Ruth Danoff

References

1. Alejandro R, Barton FB, Hering BJ, Wease S. Update from the collaborative islet transplant registry. *Transplantation*. 2008; 86:1783–1788. [PubMed: 19104422]
2. Bellin MD, Kandaswamy R, Parkey J, Zhang HJ, Liu B, Ihm SH, Ansite JD, Witson J, Bansal-Pakala P, Balamurugan AN, Papas KK, Sutherland DE, Moran A, Hering BJ. Prolonged insulin independence after islet allotransplants in recipients with type 1 diabetes. *Am J Transplant*. 2008; 8:2463–2470. [PubMed: 18808408]
3. Bishay ES, Cook DJ, El Fettouh H, Starling RC, Young JB, Smedira NG, McCarthy PM. The impact of HLA sensitization and donor cause of death in heart transplantation. *Transplantation*. 2000; 70:220–222. [PubMed: 10919608]
4. Campbell PM, Salam A, Ryan EA, Senior P, Paty BW, Bigam D, McCready T, Halpin A, Imes S, Al Saif F, Lakey JR, Shapiro AM. Pretransplant HLA antibodies are associated with reduced graft survival after clinical islet transplantation. *Am J Transplant*. 2007; 7:1242–1248. [PubMed: 17456201]
5. Campbell PM, Senior PA, Salam A, Labranche K, Bigam DL, Kneteman NM, Imes S, Halpin A, Ryan EA, Shapiro AM. High risk of sensitization after failed islet transplantation. *Am J Transplant*. 2007; 7:2311–2317. [PubMed: 17845564]
6. Cantarovich D, Vistoli F, Bignon JD. Anti-human leukocyte antigen antibodies after islet transplantation: What do they really mean? *Transplantation*. 2008; 86:204–205. [PubMed: 18645479]
7. Cardani R, Pileggi A, Ricordi C, Gomez C, Baidal DA, Ponte GG, Mineo D, Faradji RN, Froud T, Ciancio G, Esquenazi V, Burke GW 3rd, Selvaggi G, Miller J, Kenyon NS, Alejandro R. Allosensitization of islet allograft recipients. *Transplantation*. 2007; 84:1413–1427.
8. CITR Research Group. 2007 update on allogeneic islet transplantation from the Collaborative Islet Transplant Registry (CITR). *Cell Transplant*. 2009; 18:753–767. [PubMed: 19796497]
9. Ferrari-Lacraz S, Berney T, Morel P, Marangon N, Hadaya K, Demuylder-Mischler S, Pongratz G, Pernin N, Villard J. Low risk of anti-human leukocyte antigen antibody sensitization after combined kidney and islet transplantation. *Transplantation*. 2008; 86:357–359. [PubMed: 18645502]
10. Fiorina P, Shapiro AM, Ricordi C, Secchi A. The clinical impact of islet transplantation. *Am J Transplant*. 2008; 8:1990–1997. [PubMed: 18828765]
11. Fuggle SV, Martin S. Tools for human leukocyte antigen antibody detection and their application to transplanting sensitized patients. *Transplantation*. 2008; 86:384–390. [PubMed: 18698240]
12. House AA, Chang PC, Luke PP, Leckie SH, Howson WT, Ball EJ, Tan AK, Rehman F, Muirhead N, Hollomby DJ, McAlister VC, Hodsman AB, Jevnikar AM. Re-exposure to mismatched HLA

class I is a significant risk factor for graft loss: multivariable analysis of 259 kidney retransplants. *Transplantation*. 2007; 84:722–728. [PubMed: 17893605]

13. Johansson H, Lukinius A, Moberg L, Lundgren T, Berne C, Foss A, Felldin M, Kallen R, Salmela K, Tibell A, Tufveson G, Ekdahl KN, Elgue G, Korsgren O, Nilsson B. Tissue factor produced by the endocrine cells of the islets of Langerhans is associated with a negative outcome of clinical islet transplantation. *Diabetes*. 2005; 54:1755–1762. [PubMed: 15919797]
14. Kerman RH, Orosz CG, Lorber MI. Clinical relevance of anti-HLA antibodies pre and post transplant. *Am J Med Sci*. 1997; 313:275–278. [PubMed: 9145036]
15. Lobo PI, Spencer C, Simmons WD, Hagspiel KD, Angle JF, Deng S, Markmann J, Naji A, Kirk SE, Pruett T, Brayman KL. Development of anti-human leukocyte antigen class I antibodies following allogeneic islet cell transplantation. *Transplant Proc*. 2005; 37:3438–3440. [PubMed: 16298621]
16. Mohanakumar T, Narayanan K, Desai N, Ramachandran S, Shenoy S, Jendrisak M, Susskind BM, Olack B, Benshoff N, Phelan DL, Brennan DC, Fernandez LA, Odorico JS, Polonsky KS. A significant role for histocompatibility in human islet transplantation. *Transplantation*. 2006; 82:180–187. [PubMed: 16858280]
17. Naji A, Barker CF, Silvers WK. Relative vulnerability of isolated pancreatic islets, parathyroid, and skin allografts to cellular and humoral immunity. *Transplant Proc*. 1979; 11:560–562. [PubMed: 109967]
18. Olack BJ, Swanson CJ, Flavin KS, Phelan D, Brennan DC, White NH, Lacy PE, Scharp DW, Poindexter N, Mohanakumar T. Sensitization to HLA antigens in islet recipients with failing transplants. *Transplant Proc*. 1997; 29:2268–2269. [PubMed: 9193621]
19. Rickels MR, Collins HW, Naji A. Amyloid and transplanted islets. *N Engl J Med*. 2008; 359:2729. [PubMed: 19092163]
20. Rickels MR, Kamoun M, Kearns J, Markmann JF, Naji A. Evidence for allograft rejection in an islet transplant recipient and effect on beta-cell secretory capacity. *J Clin Endocrinol Metab*. 2007; 92:2410–2414. [PubMed: 17488791]
21. Rickels MR, Kearns J, Markmann E, Palanjian M, Markmann JF, Naji A, Kamoun M. HLA sensitization in islet transplantation. *Clin Transpl*. 2006:413–420. [PubMed: 18365398]
22. Ryan EA, Paty BW, Senior PA, Bigam D, Alfadhli E, Kneteman NM, Lakey JR, Shapiro AM. Five-year follow-up after clinical islet transplantation. *Diabetes*. 2005; 54:2060–2069. [PubMed: 15983207]
23. Scornik JC, Zander DS, Baz MA, Donnelly WH, Staples ED. Susceptibility of lung transplants to preformed donor-specific HLA antibodies as detected by flow cytometry. *Transplantation*. 1999; 68:1542–1546. [PubMed: 10589952]
24. Shapiro AM, Gallant HL, Hao EG, Lakey JR, McCready T, Rajotte RV, Yatscoff RW, Kneteman NM. The portal immunosuppressive storm: relevance to islet transplantation? *Ther Drug Monit*. 2005; 27:35–37. [PubMed: 15665744]
25. Stegall MD, Lafferty KJ, Kam I, Gill RG. Evidence of recurrent autoimmunity in human allogeneic islet transplantation. *Transplantation*. 1996; 61:1272–1274. [PubMed: 8610431]
26. The CITR Coordinating Center and Investigators. [accessed on March 1st 2011] The Collaborative Islet Transplant Registry Sixth annual report. [https://web.emmes.com/study/isl/reports/CITR_6th Annual Data Report 120109.pdf](https://web.emmes.com/study/isl/reports/CITR_6th_Annual_Data_Report_120109.pdf)
27. Westermarck GT, Westermarck P, Berne C, Korsgren O. Nordic Network for Clinical Islet Transplantation. Widespread amyloid deposition in transplanted human pancreatic islets. *N Engl J Med*. 2008; 359:977–979. [PubMed: 18753660]
28. Worcester Human Islet Transplantation Group. Autoimmunity after islet-cell allo transplantation. *N Engl J Med*. 2006; 355:1397–1399. [PubMed: 17005967]

Figure 1.

Changes in panel reactive antibodies (PRA) status during post-islet transplant period. Percent class I PRA after first (A, N=289), second (B, N=214) and third (C, N=76) infusions in islet alone transplant patients whose pre-transplant (Pre) PRA was below 20%. The follow-up period included 6 month (M6), 1 year (Y1), 2 year (Y2) and 3 year (Y3) post islet infusion, censored at reinfusion.

Figure 2.

Square root of class I PRA at 2 years post final islet infusion by square root of pre transplant class I PRA.

Reference lines drawn at 2.0 on both the x and y axis separate the graph into four quadrants. N = 33, 52 and 19 for recipients of 1, 2 and 3 islet infusions respectively. A large number of observations are at the 0,0 point of the graph; N = 40, 70 and 27 for recipients for 1, 2 and 3 infusions in Q1 area, 1, 0 and 0 in Q2, 2, 13 and 0 in Q3 and 2, 6 and 0 in Q4, respectively.

Figure 3. Post-transplant development of class I PRA in the presence of immunosuppression. Cumulative incidence of de novo development of >20% class I PRA is shown in 250 patients for a period of six years following first islet infusion.

Figure 4.

PRA status in islet transplant recipients with different graft outcome.

Percent class I PRA in patients without (A, N=181) or with (B, N=81) complete graft loss post-last infusion is shown. The follow-up period included pre-transplant of infusion 1 (Pre), 6 month (M6), 1 year (Y1), 2 year (Y2) and 3 year (Y3) post-last islet infusion.

Table 1

Patient demographics, islet transplant data and panel reactive antibodies (PRA) status

Factor	Summary
Number of patients	303
Age (years)	44 ± 9.7
Gender	
Male	108
Female	195
Number of islet infusions	
One	81
Two	144
Three or more	78
PRA class I	
0%	252
1–19%	37
20%	14

Table 2

Cumulative number of mismatched alleles for human leukocyte antigen (HLA) class I and II (Median with range) where patient and donor HLA are known

	1 infusion		2 infusions		3 infusions	
	N	Median	N	Median	N	Median
class I	231	3 (0 – 8)	148	6 (2 – 12)	50	9.5 (6 – 15)
class II	99	3 (0 – 6)	52	5 (0 – 11)	19	8 (3 – 14)
class I&II						
(A,B,DR)	215	5 (0 – 12)	135	9 (4 – 18)	46	14 (7 – 22)
(A,B,DR,DQ)	95	5 (0 – 13)	49	11(4 – 21)	18	17 (9 – 25)

Table 3

Post-transplant PRA $\geq 20\%$ by baseline and treatment characteristics. Patients with pre-transplant PRA $<20\%$ and at least one known post-transplant PRA measurement.

	Number of patients	N (% of total) with post-transplant PRA $\geq 20\%$	p value
Baseline PRA class I			
0	217	28 (13%)	<0.001
1–19	37	14 (38%)	
Patient received multiple islet infusions			
Yes	170	25 (15%)	0.26
No	84	17 (20%)	
Patient exposed to repeat HLA donor mismatches *			
Yes	39	3 (8%)	0.12
No	35	7 (20%)	

* Restricted to recipients of two islet infusions