



COLLABORATIVE ISLET TRANSPLANT REGISTRY (CITR)

GENERAL SUMMARY of 2008 REPORT

Background and Purpose. Islets are clusters of insulin-producing cells in the pancreas. In Type 1 diabetes mellitus (T1DM), islets are destroyed by the body's immune system. People with T1DM need to inject insulin every day to stay alive. In the United States, approximately one and a half million people have T1DM (*National Institute of Diabetes and Digestive and Kidney Diseases. National Diabetes Statistics, 2007 fact sheet.*) Although T1DM can occur at any age, it usually begins in childhood or young adulthood. Every year, 15,000 youths in the United States are newly diagnosed with T1DM.

People with T1DM and failing kidneys sometimes receive a simultaneous pancreas and kidney transplant. Individuals with severe secondary diabetic complications despite the best medical management may be eligible for solitary pancreas transplantation. Islet cell transplantation is an experimental alternative to pancreas transplantation for patients with severe hypoglycemia. Islet transplantation does not involve major surgery; generally only a local anesthetic is required. The islet transplant procedure uses insulin-producing cells (islets) taken from a donor pancreas by a complex process of extraction and purification. The resulting islet cells are placed into the liver's portal vein, where they produce insulin in response to meals and blood glucose levels as in a non-diabetic person.

The National Institute of Diabetes & Digestive & Kidney Diseases (NIDDK) funds the Collaborative Islet Transplant Registry (CITR) to collect data from North American programs. The Juvenile Diabetes Research Foundation (JDRF) has granted additional funding to include the participation of selected European and Australian centers. The mission of CITR is to expedite progress and promote safety in islet/beta cell transplantation through the collection, analysis, and communication of comprehensive and current data on all islet/beta cell transplants. Each year the Registry provides a comprehensive overview of the cumulative data from 1999. CITR Annual Reports are public and can be downloaded or requested in hard copy at www.citregistry.org.

Current islet transplant protocols are designed to test new techniques for increasing long-term success and minimizing risks of immunosuppression. Researchers hope also to determine if the usual progression of diabetes complications can be changed. Transplant centers provide information about their protocols on their own websites and at the National Library of Medicine's website www.clinicaltrials.gov. The CITR website (www.citregistry.org) also has a map of islet transplant programs throughout North America for potential participants to locate a program in their area.

Patients. Patients typically eligible for islet transplantation are those with T1DM for more than five years, are between 18 and 65 years of age, and have very poor diabetes control including severe hypoglycemia. Poor diabetes control can manifest as episodes of very low blood sugar and insulin reactions that can cause loss of consciousness and require the assistance of another person, wide swings of blood sugar levels (blood

glucose lability), and/or consistently high HbA_{1c} levels (hemoglobin with glucose attached), an indicator of poor glucose control.

Islet Allograft Transplantation Activity 1999-2007. Thirty-one North American medical centers performed at least one islet allograft transplant. The 2008 CITR report also includes data from two European centers. Combining all data, the report describes 325 islet transplant recipients. Of these recipients, most (86%) received islet-alone infusions (IA), while the others (14%) had previously received a kidney transplant and are designated islet-after-kidney (IAK) recipients. About one-quarter received only one infusion, half received two islet infusions from separate donors, a quarter received three infusions, while a very small number received four infusions (2%). Ninety percent of all individual infusions were composed of islets from a single donor, while the rest were from two donors.

Recipient Characteristics. The 325 islet recipients reported to the Registry to date meet the current general criteria for islet transplantation. At the time of their first infusion from 1999 to 2007, they ranged in age from 19 to 67 years and had T1DM for an average of 29 years. Almost all (95%) either experienced a severe episode or had an HbA_{1c} level over 7.0 prior to their islet transplant, and lacked c-peptide levels indicative of insulin secretion in the body. Almost all (98%) were either on a pump or were injecting insulin three or more times per day prior to their first islet infusion. The average insulin requirement of recipients prior to their first islet infusion was 37 units per day. Though there are no requirements regarding gender and race, about 65% of recipients were female and nearly all were white (99%).

Immunosuppression Therapy. At the time of the first infusion, the majority (59%) of IA recipients were placed on a Daclizumab, Sirolimus, and Tacrolimus immunosuppression regimen (commonly referred to as the “Edmonton Protocol”). However, in recent years (2006 and 2007), over two thirds of all islet cell transplants have involved different immunosuppression regimens. Therapies used in recent years include Alemtuzumab, Anti-thymocyte globulin, Etanercept, Efalizumab, and Methylprednisolone. MMF has been used at times in place of Sirolimus.

Graft Function. The desired outcomes of any therapy for T1D with severe hypoglycemia are elimination of severe hypoglycemic events, restoration of hypoglycemic awareness, improved control of blood glucose and, ideally, independence from injected insulin. After islet transplantation, decline of islet function and eventual loss of function are not uncommon experiences that may be followed by re-infusion, depending on various factors including the short supply of donor islets. We now have sufficient data to begin understanding the factors influencing the success or failure of transplanted islets.

Overall, 72% of all islet-alone recipients achieved insulin independence (defined as 14 or more consecutive days without insulin). While the remainder remained on insulin, their daily requirements decreased substantially. The likelihood of achieving insulin independence increases as more infusions are given. However, over time there is a steady decline in the maintenance of insulin independence. Of those who ever achieved insulin independence, 71% retained this status one year after achieving it and 52% remained insulin independent after two years. After their first infusion, increasing proportions of islet-alone recipients were re-infused: 11% within 30 days and 65% within a year.

Regardless of the total number of infusions given, the percent of recipients who are insulin independent generally decreases and those with graft loss increases over time. Measured from a recipient's last islet infusion, 13% of recipients experience total loss of islet function by six months; this rises to 42% by three years.

Factors associated with achieving insulin independence include better glycemic control prior to transplant (namely, lower HbA_{1c} or lower daily insulin requirement), greater number of islets and larger islet size, closely related procurement, processing and transplant centers, donor and recipient CMV status, and Daclizumab given at infusion. Factors protective against complete islet failure include older recipients with longer diabetes duration, closely related processing and transplant centers, islets with higher viability index, and use of etanercept or calcineurin. Certain other factors cannot be ruled out as important. Analyses of factors associated with outcomes will continue to be validated as the Registry data grows and matures.

Severe Hypoglycemia and HbA_{1c}. The percent of recipients with HbA_{1c} < 6.5 and no severe hypoglycemic events increases remarkably from 2% pre-transplant to about 60% by one year after last infusion. Importantly, participants who experienced a severe hypoglycemic event during follow-up were on insulin at the time of the event. Hypoglycemia awareness is also markedly improved in recipients as long as they retain at least some graft function.

Medications. Islet transplantation increases blood pressure and lipid levels. Prior to their first infusion, 41% of the recipients were on at least one anti-hypertensive medication and 32% were on a lipid lowering medication. One year after last islet infusion, these rates increased to 52% and 61%, respectively.

Adverse Events. Sixty-four percent of the islet alone recipients experienced at least one adverse event in the year following their first infusion that was deemed related to the islet infusion or immunosuppression medication; 34% experienced one or more serious adverse events that were infusion or immunosuppression related in this same period.

The most common serious adverse events within the first year following an islet allograft infusion are: elevated liver function tests (9% of all allograft recipients) and neutropenia (9%), followed by procedural hemorrhage (6%), abdominal pain (4%), and pneumonia (3%). Anemia, diarrhea, hypoglycemia, portal vein thrombosis, vomiting, cholecystitis, and lymphopenia occur less frequently (2% each). The vast majority of adverse events resolved with no long-term effects.

Neoplasms have been diagnosed in 14 of the 325 islet recipients. None were related to the islet infusion procedure while four may have been related to the immunosuppression therapy (basal cell carcinoma, squamous cell carcinoma, ovarian cysts, and papillary thyroid cancer). The most frequent type of neoplasm was squamous cell carcinoma (six recipients). Ten recipients continued their islet transplant immunosuppression regimen; two withdrew voluntarily; and two have missing follow-up.

There have been seven deaths reported to the Registry in islet allograft recipients; a viral meningitis-attributed death possibly related to the immunosuppressant therapy occurring more than three years following the person's second islet infusion; a drug toxicity (acute methadone and diphenhydramine) 70 days after the person's third infusion; a stroke more than two years after the person's second infusion; another stroke more than three years after the recipient's only islet infusion, and three deaths due to unknown causes (discovered in obituaries).

Conclusions. Compared to 2005, half as many North American centers performed an islet transplant and there were one third as many islet transplant recipients in 2007. However, with the start of new clinical trials in 2008, the number of new islet cell recipients is expected to rise. Islet transplantation continues to show short-term benefits of insulin independence, remarkable reductions in HbA_{1C} levels, elimination of severe hypoglycemic episodes as long as there is islet function, and a return of hypoglycemia awareness. The current data suggests that the best candidates for islet transplantation are those with better glycemic control to start with, and that more and larger islets lead to better outcomes. As islet transplantation evolves, long-term benefits and safety will continue to be monitored.

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