citr
Collaborative Islet Transplant Registry

COLLABORATIVE ISLET TRANSPLANT REGISTRY (CITR)

GENERAL SUMMARY of 2009 REPORT

Background and Purpose. Islets are found in the pancreas and produce insulin. 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 1999-2008. The 2009 CITR report includes data from 27 North American, three European, and two Australian centers. Combining all data, the report describes 412 islet transplant recipients. Of these recipients, most (84%) received islet-alone infusions (IA), while the others (16%) 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%).

Recipient Characteristics. At the time of their first infusion from 1999 to 2008, recipients ranged in age from 19 to 67 years and had T1DM for an average of 28 years. Almost all (95%) either experienced a severe episode or had an HbA_{1C} level over 7.0 prior to their islet transplant. Almost all (97%) were either on an insulin 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 63% of recipients were female and nearly all were white (99%).

Immunosuppression Therapy. At the time of the first infusion, the majority (52%) of IA recipients were placed on a Daclizumab, Sirolimus, and Tacrolimus immunosuppression regimen (commonly referred to as the "Edmonton Protocol"). However, in recent years (2007 and 2008), 88% of all islet cell transplants have involved different immunosuppression regimens. Therapies used in recent years include Alemtuzumab, Anti-thymocyte globulin, Etanercept, Efalizumab, Basiliximab, 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, 70% of all 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, 70% retained this status one year after achieving it and 55% remained insulin independent after two years.

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, 12% of recipients experience total loss of islet function by six months; this rises to 35% 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 infused, and closely related procurement, processing and transplant

centers. Factors protective against complete islet failure include older recipients and closely related processing and transplant centers. 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 56% 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, 43% of the recipients were on at least one anti-hypertensive medication and 34% were on a lipid lowering medication. One year after last islet infusion, these rates increased to 53% and 61%, respectively.

Adverse Events. Fifty 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; 32% 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: neutropenia (8% of all allograft recipients), elevated serum creatinine (8%) and elevated liver function tests (7%), followed by procedural hemorrhage (6%), abdominal pain (4%), pneumonia (3%), diarrhea (3%), and hypoglycemia (3%). Anemia, portal vein thrombosis, vomiting, leukopenia, and lymphopenia occur less frequently (2% each). The vast majority of adverse events resolved with no long-term effects.

Neoplasms have been diagnosed in 21 of the 412 islet recipients. None were related to the islet infusion procedure while nine may have been related to the immunosuppression therapy (basal cell carcinoma (x2), squamous cell carcinoma (x3), breast cancer, ovarian cysts, and papillary thyroid cancer (x2)). The most frequent type of neoplasm was squamous cell carcinoma (nine recipients). Seventeen recipients continued their islet transplant immunosuppression regimen; two withdrew voluntarily; and two have missing follow-up.

There have been nine deaths reported to the Registry in islet allograft recipients; a viral meningitis-attributed death possibly related to the immunosuppressant therapy occurring three years following the person's last islet infusion; a drug toxicity (acute methadone and diphenhydramine) 70 days after last infusion; a stroke two years after last infusion; another stroke three years after last islet infusion, a death due to acute respiratory distress syndrome five years post last islet infusion, pneumonia eight years after last islet infusion, diabetic ketoacidosis six years after last infusion, atherosclerotic coronary artery disease 16 months post last infusion, and one death due to unknown causes (discovered in obituaries).

Conclusions. Compared to 2005, fewer North American centers performed an islet transplant and there were half as many islet transplant recipients in 2008. However, more centers transplanted and more people received an islet transplant in 2008 compared to 2007. With the continued expansion of clinical trials started in 2008, the

number of new islet cell recipients will continue to rise. Islet transplantation shows short-term benefits of insulin independence, remarkable reductions in HbA_{1C} levels, elimination of severe hypoglycemic episodes, 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. Close relationships between procurement, processing, and transplant teams are associated with favorable outcomes. As islet transplantation evolves, long-term benefits and safety will continue to be monitored.

Prepared by:
CITR Coordinating Center
The EMMES Corporation, Rockville, MD
www.CITRegistry.org

November 2009

The Collaborative Islet Transplant Registry (CITR) is sponsored by the National Institute of Diabetes & Digestive & Kidney Diseases under contract number N01-DK-6-2868 to The EMMES Corporation. Reprints and additional information may be requested via email to citr@emmes.com or through the CITR website at www.citregistry.org.