



2006 Executive Summary of the Collaborative Islet Transplant Registry (CITR)

Islets are clusters of insulin-producing cells located in the pancreas. In patients with Type 1 diabetes mellitus (T1DM) all islets are destroyed by an autoimmune attack and patients need to inject insulin every day to stay alive. The total prevalence of diagnosed T1DM in the United States (US) (all ages, 2004) is approximately 650,000-1,300,000 people. For patients with T1DM and poor kidney function, a whole pancreas transplant is sometimes performed. An alternative procedure uses insulin-producing cells (islets) extracted from a donor pancreas. These are implanted, typically by infusion via the portal vein into the liver, so that the islets produce insulin as needed by the recipient.

Islet transplantation is an experimental procedure in the US that is regulated by the Food and Drug Administration (FDA). Approximately, 40 transplant programs in the US are conducting this procedure, or are in the process of starting a program. Typical patients eligible for this procedure include those who have T1DM for more than five years, are between 18 and 65 years of age, and have poor diabetes control despite intensive efforts being made in close collaboration with a qualified diabetes care team. Poor diabetes control can manifest as frequent episodes of critically low blood sugar levels (hypoglycemic episodes and insulin reactions) requiring the assistance of another person, wide swings of blood sugar levels (blood glucose lability), or consistently high HbA_{1C} levels (>8%).

Most ongoing studies differ minimally in the entry criteria for patients and in the types of immunosuppression therapy used to prevent rejection of the islet cells in the body. It is the goal of these studies to help determine if improvement in the glycemic control and/or reversal of insulin dependency can be achieved, to assess the long-term function of successful islet transplants and risks of associated immunosuppressive medication, and if the natural history of diabetes complications is altered.

To accumulate and compile the data from all completed and ongoing studies since 1999, the National Institute of Diabetes & Digestive & Kidney Diseases funded the Collaborative Islet Transplant Registry (CITR). 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 performed in North America. Each year the Registry provides a complete analysis of the cumulative data. The third report, published in 2006, summarizes information on patients who received one or more islet cell transplants between 1999 and 2005. All CITR reports are public and can be downloaded or requested in hard copy at www.citregistry.org.

The focus of the Registry is the collection and analysis of islet allograft transplants. In a survey of all North American transplant programs, 31 active programs reported 593 islet infusion procedures in 319 recipients during 1999-2005. CITR has information on 225 of the 319 allograft recipients (71%) and 425 of the 593 infusion procedures (72%) from 23 participating centers. Sixty-four of the recipients (28.4%) received just one islet infusion, 122 (54.2%)

received two, 38 (16.9%) received three, and one (0.4%), received a total of four islet infusions. On average, recipients received a total of 814,378 (SD 368,620) total islet equivalents (IEQs), or 12,486 IEQs/kilogram body weight (SD 5,731).

Of the 225 recipients, 203 (89%) were participants without a previous kidney transplant who received an islet infusion(s) (islet transplant alone recipients), while 22 recipients (10%) had previously received a kidney transplant and received an islet infusion(s) after a kidney transplant. For the 203 islet transplant alone recipients, the median age of the islet transplant recipient is 42.3 years (range 23.0 to 65.1) and the median duration of diabetes is 29 years (range 4 to 51). The median weight of the participant is 65 kg (range 35.0 to 98.1) and the median body mass index (BMI) is 23.3 kg/m² (range 15.5 to 31.6). Over 68% of the recipients are female and they have limited racial and ethnic diversity. At baseline, over 89% of the recipients have a basal C-peptide < 0.5 ng/mL (C-peptide results at the time closest to transplant were used for this analysis and do not necessarily represent the typical values for a participant) and over 78% have an HbA_{1c} > 6.5%.

The majority of recipients (61.1%) began an immunosuppression therapy regimen of sirolimus, tacrolimus, and daclizumab at the time of their first infusion procedure; for an additional 8.4%, infliximab was added to the regimen.

Over 65% of recipients achieve insulin independence at least once (for a period of 14 or more days). Only 28.7% of recipients achieve this independence with one infusion, while recipients of two infusions and three infusions achieve insulin independence more readily (56.1% and 51.1%, respectively). For those achieving insulin independence, 67.5% remain free of insulin replacement therapy one year after first achieving insulin independence, and 43.3% remain free from insulin replacement therapy at two years. For those receiving insulin therapy, mean insulin use at 6 and 12 months post last infusion was reduced to 50% of pre-infusion levels.

Following the first infusion procedure, most recipients become C-peptide positive and have better control of their glucose levels. At one year following the last infusion procedure, recipients who have ever achieved insulin independence have a mean fasting blood glucose of 111.5 mg/dL (SD 30.4), a basal C-peptide of 1.1 ng/mL (SD 0.65) and an HbA_{1c} of 6.0% (SD 0.8). Those who never achieved insulin independence have a higher fasting blood glucose (122.5 mg/dL, SD 61.0) and HbA_{1c} (6.5%, SD 1.0), and a lower C-peptide (0.41 ng/mL, SD 0.48).

There is a dramatic decrease in the number of severe hypoglycemic events following islet transplant. One hundred and seventy-one recipients (84.2%) reported having one or more severe hypoglycemic episodes that required assistance in the year prior to their first islet infusion. During the first six months following the first infusion only six recipients reported a severe event and only five recipients reported a severe event during months 6-12. Each of these recipients was on insulin replacement therapy at the time of the severe hypoglycemic episode.

For 121 participants with complete reporting of changes in islet graft function, there have been a total of 32 recipients (26.4%) who have experienced islet graft failure. On average, complete loss of islet function occurred in these 32 recipients 506 days (SD 429 days) after receiving their first infusion, while the median time to complete loss of islet function is 385 days.

A total of 236 severe adverse events were reported for the 203 recipients. Of these 236 serious adverse events, 186 of the events (78.8%) were reported during the first year following their first islet infusion procedure, suggesting that most serious adverse events occur during this period. Similarly, about half of the recipients (96/203; 47.3%) experienced a serious adverse event in the first year. The local CITR Investigator attributes cause of the event to either the islet infusion procedure and/or to the immunosuppression therapy. Of the 236 serious adverse events, 33% were related to the infusion procedure, 25% were related to the immunosuppression therapy, 2% were related to both the infusion procedure and the immunosuppression therapy, and 40% were not related to either the infusion procedure or to the immunosuppression therapy.

The most commonly reported serious adverse events included elevated liver function tests (21.2%), neutropenia (10.6%), procedural related bleeds/portal vein thrombosis (9.7%) and abdominal pain (5.5%). There were four reports of death not attributed to the islet infusion procedure or to the immunosuppression therapy.

Of the 236 serious adverse events, 93.6% (N=221) resolved with no residual effects, 2.5% (N=6) remained in a persistent condition, 2.1% (N=5) resolved with sequelae, 0.8% (N=2) was attributed to death (one additional death occurred but was not reported via the Adverse Event form), and 0.8% were missing information on the serious adverse event outcome.

Islet transplantation continues to evolve and short-term benefits of islet transplantation such as normal or near normal HbA_{1C} levels in the absence of hypoglycemic episodes have been demonstrated by an ever-increasing number of transplant centers. The long-term safety and efficacy profile of islet transplantation and immunosuppression and the effects of islet transplantation on secondary complications are less well understood and are the focus of current research. With continued participation of the existing and new islet transplant programs, CITR expects, through expeditious analyses and Annual Reports, to assist the islet transplant community in the continued development of islet transplantation into a vital therapy of selected patients with T1DM.

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