

COLLABORATIVE ISLET TRANSPLANT REGISTRY (CITR)

EXECUTIVE SUMMARY of 2007 REPORT

Background and Purpose. Islets of Langerhans 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 IDDM in the United States (US) (all ages, 2005) is approximately 1,400,000 - 2,800,000 people (<http://diabetes/niddk/nih.gov/dm/pubs/statistics>). For patients with T1DM and poor kidney function, a whole pancreas transplant is sometimes performed. For patients with severe hypoglycemia, an alternative experimental procedure uses insulin-producing cells (islets) extracted from a donor pancreas. These are implanted typically into the liver's portal vein, where the islets produce insulin as needed by the recipient.

The National Institute of Diabetes & Digestive & Kidney Diseases (NIDDK) funds the Collaborative Islet Transplant Registry (CITR) for data collection from North American programs. The Juvenile Diabetes Foundation 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.citrregistry.org.

Most ongoing protocols are experimental and designed to identify factors of long-term success and risks of immunosuppression, and determine if the natural history of diabetes complications can be altered. Each center publishes the results of their studies independently and provides information regarding their open protocols through their own means and/or at the National Library of Medicine's website www.clinicaltrials.gov.

Patients. Patients typically eligible for islet transplantation are those who have 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 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, an indicator of poor glucose control.

Islet Allograft Transplantation Activity 1999-2006. Thirty-one North American medical centers performed at least one islet allograft transplant. The 2007 report also includes data from one European center whose participation began in 2006. Combining the data from the North American and European centers, the CITR database comprises 292 allograft recipients registered through December 31, 2006, and 579 infusion procedures derived from a total of 634 donors. Of all allograft recipients, 262 (90%) received one to four islet-alone infusions (IA), while 30 recipients (10%) had previously received a kidney transplant and are designated islet-after-kidney (IAK) recipients.

Recipient Characteristics. The average age of islet allograft transplant recipients in CITR is 43.7 years (range 19-67) and the average duration of diabetes is 29 years (range 5 to 53). The average weight of the participant is 66 kg (range 35 to 98) and the average body mass index (BMI) is 23.7 kg/m² (range 15 to 37). About 64% of the participants are female. There is limited racial and ethnic diversity among the participants with this data reported.

Approximately 37% of the 292 allograft islet transplant participants were on an insulin pump prior to their first infusion and 98% of the participants were on the pump or were taking three or more insulin injections per day. At baseline, 91% of the participants had a basal C-peptide < 0.5 ng/mL and 81% had a HbA_{1C} > 6.5%. C-peptide levels are a marker of insulin secretion in the body. The average daily insulin requirement of participants prior to their first infusion procedure was 36.9 units and those on intensive insulin therapy had received intensive therapy for an average of 18.7 years.

Compared to recipients of a single infusion, recipients of three infusions were taking a higher baseline daily insulin dose, had a higher HbA_{1C} and had a lower PRA percentage.

Immunosuppression Therapy. The majority (60%) of the IA recipients at the time of first infusion were on a Daclizumab, Sirolimus, and Tacrolimus immunosuppression regimen. Daclizumab was used for 80% of IA first infusions. Anti-thymocyte globulin was given alone or in combination in 11% of first infusions.

Graft Function. After the first infusion, increasing proportions of islet-alone recipients are re-infused: 12% by Day 30, 37% by Day 75, 57% by Month 6, and 69% by Year 1. Seventy-six of the recipients (26%) received a single islet infusion, 149 (51%) received two, 63 (22%) received three, and four (1%) received a total of four islet infusions. On average, recipients received a total of 819,160 total islet equivalents (IEQs), or 12,669 IEQs/kilogram body weight.

Overall, 67% of allograft recipients achieve insulin independence (defined as 14 or more consecutive days without insulin) at least once in the first year after first infusion, and by Year 2 this increases to 73%. The more infusions are given, the higher the likelihood of achieving insulin independence. However, over time there is a steady decline in the maintenance of insulin independence. For all participants who ever achieved insulin independence, only 67% have retained this status one year after achieving it and this decreases to 45% at two years.

Of all IA recipients, at three-years after first infusion, regardless of the total number of infusions received, about 16% are insulin independent, 28% are insulin dependent with detectable C-peptide, 32% have no detectable C-peptide or are lost to follow-up, and 23% have missing data (required but not yet reported).

Beginning at the recipient's last islet infusion, insulin independence declines steadily from 46% at Month 6 to 16% at Year 3, while a stable 18-22% retain graft function with reduced requirements of injected insulin over the three years. The proportion with total loss of islet function increases steadily from 13% at Month 6 to 42% at Year 3 after last infusion. Regardless of the total number of infusions given, insulin independence decreases and graft loss increases over time. However, long-term graft function is more likely in recipients who achieve insulin independence at any time after their one to several islet infusions.

C-peptide levels are substantially increased by islet transplantation.

Factors associated with achieving insulin independence included lower HbA_{1C} and more total islet equivalents infused. Factors protective against complete islet failure include more infusions given, older recipients and/or longer diabetes duration, higher stimulation index of the islets, and etanercept given at induction. These results must be regarded as preliminary. Analyses of factors associated with outcomes have just begun and will continue to be validated as the Registry data grows and matures.

HbA_{1C}. HbA_{1C} levels are improved substantially by islet transplantation. The percent of IA recipients with HbA_{1C} < 7.0% increases from 28% pre-infusion to 59-75% at Month 6 and 53-67% at Year 3 after last infusion.

Severe Hypoglycemic Events. The percent of recipients experiencing severe hypoglycemic events after islet transplantation is reduced from 76-87% pre-infusion to less than 20% throughout the first year after last infusion, and to 9-43% at three years after last infusion. Hypoglycemia awareness is also markedly improved in recipients with graft function. All participants who experienced a severe hypoglycemic event during follow-up were on insulin at the time of the event.

Medications. Prior to the first infusion, 40% of the recipients were on at least one anti-hypertensive medication and 31% were on a lipid lowering medication. By Year 1 after last infusion, these rates increased to 48% and 61%, respectively.

Adverse Events. Fifty-four percent of the islet alone recipients experienced at least one adverse event in the year following their first infusion that was related to the islet infusion or immunosuppression medication; 32% experienced one or more serious adverse event that was infusion or immunosuppression related in this same period.

Overall, a total of 337 serious adverse events were reported to the Registry, with 40% described as life threatening and 46% requiring an inpatient hospitalization. Seventy percent (236 of 337) of serious adverse events occurred in the first year following the participants' first infusion procedure. About 32% of all serious adverse events were classified by the reporting CITR investigator as related to the islet infusion procedure and 25% related to the immunosuppression therapy. Approximately 91% of the serious adverse events resolved with no residual effects.

Reports of neoplasms have been received in ten recipients. They all received treatment. Five resolved with no residual effects, four with sequelae and one is pending final outcome.

There have been four reports of death to the Registry; a viral meningitis attributed death 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 and a death due to unknown causes (discovered in obituaries) more than four years after the person's second infusion. The primary investigators at these medical centers do not attribute the islet infusion for immunosuppression medication as the cause of any of these deaths.

Conclusions. Islet transplantation continues to show short-term benefits of insulin independence, normal or near normal HbA_{1c} levels, and sustained marked decrease in hypoglycemic episodes. Long-term benefits and safety of immunosuppression are less well understood and are the focus of ongoing research. The Registry is growing large enough to begin investigating factors predictive of success.

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