Background. This report summarizes the primary efficacy and the safety outcomes of islet transplantation reported to the NIDDK and JDRF funded Collaborative Islet Transplant Registry (CITR), currently the most comprehensive collection of human-to-human islet transplant data.

Methods. CITR collects and monitors comprehensive data on alogeneic islet transplantation in North America, Europe, and Australia since 1999.

Results. As of April 2008, the CITR registry comprised 325 adult recipients of 649 islet infusions derived from 712 donors. At 3 years post-first infusion, 23% of islet-alone recipients were insulin independent (II, ≥2 weeks), 29% were insulin dependent with detectable C-peptide, 26% had lost function, and 22% had missing data. Seventy percent achieved II at least once, of whom 71% were still II 1 year later and 52% at 2 years. Higher number of infusions, greater number of total islet equivalents infused, lower pretransplant HbA1c levels, processing centers related to the transplant center, and larger islet size are factors that favor the primary outcomes. Protocols with daclizumab or etanercept during induction had higher rates of II and lower rates of function loss, which endorse the current approaches. Infusion-related adverse event incidence was 0.71 events/person-year (EPY) in year 1, whereas immunosuppression-related adverse event incidence was 0.87 EPY, both declining to less than 0.21 EPY thereafter.

Conclusions. Clinical islet transplantation needs to be evaluated using the most clinically relevant endpoints such as glucose stabilization and severe hypoglycemia prevention. The cumulative results of the registry confirm the inarguably positive impact of islet transplantation on metabolic control in T1 diabetes.

Keywords: Islet transplantation, T1 Diabetes, Immunosuppression.

(Transplantation 2008;86: 1783–1788)
Statistics

Results are shown either in aggregate or by islet-alone (IA) or islet-after-kidney recipients. Descriptive statistics include distribution summary statistics such as mean and standard deviation or median and interquartile range for continuous variables, or distributions/bar charts for categorical variables.

The Cox regressions represent our current approach to statistical modeling to identify factors that may be predictive of the primary outcomes. Factors that could change with additional infusions were cumulated or averaged over all infusions. The factors are summarized in Supplementary Materials to the 2008 CITR Annual Report. Factors available on more than 70% of the study group were included in multivariate models; those that could not be so included could not be ruled out. Cox hazard ratios less than one indicate a lower likelihood of the event with higher levels of the factor. Binary factors are coded 0 = absent and 1 = present. Univariate models are used first to characterize all possible effects. Any factor with a nominal univariate significance level of $P < 0.10$ was a candidate for a multivariate model. In addition to uncontrollable imbalance among baseline recipient factors, islet procurement and preparation factors and immunosuppression regimens, as well as the difficulty in characterizing factors over two or three infusions, multivariate modeling was also hampered by the relatively small size of the overall study group, competing risks among the primary outcomes and the influence of managed or uncontrollable factors such as decision to reinfuse or availability of islets. Thus, the aim of multivariate modeling was to eliminate duplicative information within the broad categories of factors and to rule in factors with sufficient power to be detected. Variables significant univariately but missing so often that they could not be included in the multivariate models cannot be ruled out.

Primary outcomes after first infusion are as follows: immediate islet cell failure (primary nonfunction), insulin dependence, insulin independence (II ≥ 2 weeks), graft loss, or reinfusion. Events occurring after first infusion are censored at reinfusion, current follow-up or complete graft loss, whichever occurs first, which are presented in the 2008 Annual Report. The same outcome states except reinfusion are also modeled following the last of a series of infusions, in which factors of recovery, donor, and islets are summarized or averaged over all infusions presented herein.

RESULTS

Islet Allograft Transplantation Activity 1999 to 2007

Figure 1(A) shows the number of active US/Canadian islet transplant centers by year, comprising all but one of the human-to-human islet transplant programs in North America active in this period. The number of US/Canadian islet...
transplant centers has declined considerably since the peak in 2005. Figure 1(B) shows the number of US/Canadian islet transplant recipients (first infusion) by year from the 31 islet transplant sites. The Registry data include 78% of the estimated total US/Canadian recipients. Two European centers joined the registry in 2006 and contributed data for this report.

As of April 1, 2008 the CITR registry comprised 325 allograft recipients of 649 infusion procedures derived from a total of 712 donors. Of the 325 recipients, 279 (86%) were recipients of IA infusions, whereas 46 recipients (14%) had previously received a kidney transplant (islet-after-kidney). Eighty-four (26%) received a single infusion, 164 (50%) received two, 71 (22%) received three, and six (2%) received four.

**Recipient, Procurement, Donor, Islet Characteristics, and Immunosuppression Therapies**

Recipient, procurement, donor, islet characteristics, and immunosuppression therapies are detailed in the 2008 Annual Report (4). For the Cox models of outcomes, individual immunosuppressant therapies were evaluated as given or not given as well as combinations as defined by local protocols, some of which may have been given at more than one center.

**Severe Hypoglycemia and HbA1c**

Islet transplantation dramatically reduces the occurrence of severe hypoglycemic events and substantially improves HbA1c levels (Fig. 2A). The percent of IA recipients with HbA1c less than 6.5% and absence of severe hypoglycemic episodes increases from 2% preinfusion to 47% to 69% at year 1 post-last infusion. Hypoglycemia awareness is also markedly improved and is eroded only by loss of graft function or to follow-up (Fig. 2B).

**Graft Function**

The percent of IA recipients with C-peptide more than 0.5 ng/mL increases from 8% preinfusion to 47% at month 6...
and 43% at year 1 post-first infusion, with 32% retaining this level of function at year 3 post-last infusion. After the first infusion, increasing proportions of IA recipients were reinfused: 11% by day 30, 34% by day 75, 53% by month 6, and 65% by year 1. Of 198 IA recipients expected at 3-years post-first infusion, 23% were II, 29% were insulin dependent with detectable C-peptide, 26% had no detectable C-peptide (including those known to have lost islet function), and 22% had missing data. Five of IA allograft recipients experienced primary nonfunction (one after each of two infusions).

After last infusion, the proportion of IA recipients with loss of islet function (observed/reporting graft failure or no detectable C-peptide) increased steadily from 10% at month 6 to 34% at year 3. A stable 23% to 26% retained graft function with exogenous insulin over the 3 years; the percentage of missing data increases over time. II prevalence peaked at 65% at month 4 and then declined to approximately 24% at year 3 post-last infusion. Seventy percent achieved II at least once after first infusion, comprising all those with one or multiple infusions (Fig. 2C). Of these, 71% were still II 1 year later and 52% at 2 years (Fig. 2D), translating to 50% achieving and retaining II for 1 year and 35% for 2 years for all IA recipients.

Factors of Primary Endpoints Post-first and Post-last Infusion

Table 1 shows the factors significantly associated (P<0.10) multivariately with II post-last infusion (174 events of 264 cases). Lower pretransplant HbA1c levels, processing centers related to the transplant center; larger islet size (estimated by IEQs/total particles at time of islet counting) and daclizumab favor achieving II. Donor Hispanicity is correlated with body mass index, being given insulin or steroids, and various human leukocyte antigen mismatches: these in turn predict less favorable outcomes. Factors that cannot be ruled out as important include donor(s) receiving steroids, human leukocyte antigen factors, and immunosuppression combinations.

<table>
<thead>
<tr>
<th>TABLE 1. Factors of insulin independence and complete islet failure post-last infusion</th>
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<tr>
<td>Final multivariate model</td>
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<tr>
<td>Factors of insulin independence</td>
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<td>Factors of complete islet failure</td>
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<td>Viability &gt;87%</td>
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<tr>
<td>Etanercept</td>
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<td>Calcineurin inhibitor</td>
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HR, hazard ratio.

There is too much imbalance between many of the immunosuppressant regimens and most measures of islet procurement and processing to allow meaningful multivariate adjustment.

In the final model for complete islet failure post-last infusion based on 78 events of 264 (Table 1), older recipient age, related processing and infusion centers, islet viability more than 78%, and etanercept or calcineurin inhibitor use predict lower risk of losing the graft. Variables that could not be ruled out as protective against graft failure include larger islet size, lower baseline HbA1c, and negative IA-2 autoantibody.

Metabolic Measures

Fasting plasma glucose values and HbA1c substantially decrease over time, whereas C-peptide values substantially increase. These results are affected by the recipients’ transient insulin status and total number of infusions, and strongly associated with achievement of II.

Lipid Lowering and Antihypertensive Medications

Before the first infusion, 41% of the recipients were on at least one antihypertensive medication and 32% were on a lipid lowering medication. By year 1 post-last infusion, these rates increased to 52% (P=0.04) and 61% (P<0.001), respectively.

Laboratory Measurements

Incidence of two times or greater than the upper limit of normal at CITR scheduled follow-up was 5% for alanine aminotransferase, 4% for aspartate aminotransferase, 10% for alkaline phosphatase, and 1% for total bilirubin. There were no instances at this level for total cholesterol and 4% incidence for triglycerides. There were 46 reports (16%) of a participant with an increase in serum creatinine of greater than 0.5 mg/dL above their baseline level.

Adverse Events

For IA recipients, the incidence per follow-up year of AEs classified as definitely or probably related to the infusion procedure ranged from 0.14 to 0.64 events/person-year, peaking in 2002; the incidence of infusion-related severe AEs ranged from 0.06 to 0.36/person-year, peaking also in 2002. The infusion-related incidence of AEs was highest in the first follow-up year post-first infusion (0.71, 95% confidence interval [CI] 0.61–0.82) declining to less than 0.07/follow-up year thereafter. The incidence of infusion-related SAEs also peaks in the first year postinfusion, declining rapidly thereafter. Because of the peak of first infusions in 2005, the first year of follow-up is confounded with calendar year; many events having occurred in the first follow-up year, most of which were in 2002 to 2005. Of the total 111 SAEs, one did not resolve (portal vein thrombosis requiring continued anticoagulation), one resolved with sequelae (myonecrosis), and the remainder resolved with no sequelae.

In IA recipients, the incidence per follow-up year of AEs classified as definitely or possibly related to immunosuppression therapy peaked in the first year postinfusion (0.87, 95% CI 0.76–0.99), with 0.28 serious AE/person-year (95% CI 0.22–0.35), which declined to less than 0.21 event/person-year in follow-up years 2 to 5. Of the 96 serious AEs possibly or definitely related to immunosuppression, one resulted in death (viral meningitis), seven resolved with sequelae, six re-
solved with persistent condition, and the remainder resolved with no residual effects.

The most common serious AEs within the first year after an islet allograft infusion are as follows: 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).

**Neoplasms**

Neoplasms occurred in 14 allograft recipients. None were classified as related to the islet infusion procedure. Four were classified as possibly or definitely related to the immune suppression medication (basal cell carcinoma, squamous cell carcinoma, ovarian cysts, and papillary thyroid cancer). Eleven continued the islet transplant immunosuppression protocol, one withdrew voluntarily (squamous cell carcinoma at 20 months post-second infusion), and two have missing follow-up.

**Reported Deaths**

There have been seven reports of death among allograft recipients: a viral meningitis possibly related to the immunosuppressant therapy occurring more than 3 years after the person’s second islet infusion, a drug toxicity (acute methadone and diphenhydramine) 70 days post-third infusion, a stroke more than 2 years post-second infusion, another stroke more than 3 years post-single infusion, and three deaths due to unknown causes.

**DISCUSSION**

Despite the substantial decline of new islet allograft recipients in 2007 to 2008, the CITR registry continues to represent the most comprehensive collection of the human islet transplantation experience since 1999. The updated data confirm the chief benefits of islet transplantation previously described: stabilization of glucose metabolism, sustained decrease in severe hypoglycemic episodes, restoration of symptoms awareness, and reduction of HbA1C to less than 6.5 for at least 50% of the recipients at 1 year.

Because of the rigorous monitoring of the data to achieve 21 CFR compliance, CITR provides the most accurate description of AEs experienced by islet recipients. The incidence of serious AEs related to infusion procedure or to effects of the immunosuppressive regimens is now characterized as less than one event per person year in the first year postinfusion, with marked decline after that period. All but a small number of AEs were resolved without sequelae, thus confirming the overall relative safety of the procedure and therapy. No additional deaths or neoplasms have been reported since the last update (4).

The analysis of factors associated with islet graft function over multiple infusions has few analogues in the transplantation field. Factors that are definitely contributory, as well as factors that cannot be ruled out include the following: higher number of islet infusions, greater number of total IEQs infused, older recipient age, lower recipient HbA1C levels, related processing/infusion centers, islet viability more than 87%, larger islet size and use of daclizumab, etanercept, or calcineurin inhibitors are favorable factors. Giving donors steroid in-hospital negatively affected II achievement, although this is correlated with insulin requirement, reflecting lower beta-cell secretion capacity as in in vivo models of increased insulin demands. Protocols with daclizumab or etanercept during induction had higher rates of II and lower rates of function loss, respectively, which endorse the current approaches.

Clinical islet transplantation deserves clinically relevant endpoints such as glucose stabilization and severe hypoglycemia prevention. The cumulative results of the registry confirm the inarguably positive impact of islet transplantation on metabolic control in T1D. Missing data, especially in later years of follow-up, and lack of experimental control are limitations.

**CONCLUSIONS**

From 1999 to 2007, the chief clinical benefits of human islets transplantation included a remarkable reduction in the occurrence of severe hypoglycemia and a success rate of 70% in achievement of II, which persists for 2 years or more in 50% of those achieving II, or 35% of all IA recipients. These results are consistent throughout the 8 years of follow-up included in the registry. Factors associated with primary outcomes identified should guide researchers in designing more effective and safer protocols, leading toward approval in the United States and enhanced efficacy of clinical islet transplantation.

**APPENDIX**

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REFERENCES


