Improvement in Outcomes of Clinical Islet Transplantation: 1999-2010

Franca B. Barton, EMMES Corp
Michael R. Rickels, University of Pennsylvania
Rodolfo Alejandro, University of Miami
Bernhard J. Hering, University of Minnesota
Stephen Wease, The EMMES Corporation
Bashoo Naziruddin, Baylor University
Jose Oberholzer, University of Illinois at Chicago
Jon S. Odorico, University of Wisconsin
Marc R. Garfinkel, Southern Illinois University
Marlon Levy, University of Texas Dallas

Only first 10 authors above; see publication for full author list.

Journal Title: Diabetes Care
Volume: Volume 35, Number 7
Publisher: American Diabetes Association | 2012-07-01, Pages 1436-1445
Type of Work: Article | Final Publisher PDF
Publisher DOI: 10.2337/dc12-0063
Permanent URL: https://pid.emory.edu/ark:/25593/s5jb5

Final published version: http://dx.doi.org/10.2337/dc12-0063

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Accessed December 6, 2018 8:24 PM EST
Improvement in Outcomes of Clinical Islet Transplantation: 1999–2010

OBJECTIVE—To describe trends of primary efficacy and safety outcomes of islet transplantation in type 1 diabetes recipients with severe hypoglycemia from the Collaborative Islet Transplant Registry (CITR) from 1999 to 2010.

RESEARCH DESIGN AND METHODS—A total of 677 islet transplant-alone or islet-after-kidney recipients with type 1 diabetes in the CITR were analyzed for five primary efficacy outcomes and overall safety to identify any differences by early (1999–2002), mid (2003–2006), or recent (2007–2010) transplant era based on annual follow-up to 5 years.

RESULTS—Insulin independence at 3 years after transplant improved from 27% in the early era (1999–2002, n = 214) to 37% in the mid (2003–2006, n = 253) and to 44% in the most recent era (2007–2010, n = 208, P = 0.006 for years-by-era; P = 0.01 for era alone). C-peptide ≥0.3 ng/mL, indicative of islet graft function, was retained longer in the most recent era (P < 0.001). Reduction of HbA1c and resolution of severe hypoglycemia exhibited enduring long-term effects. Fasting blood glucose stabilization also showed improvements in the most recent era. There were also modest reductions in the occurrence of adverse events. The islet reinfusion rate was lower: 48% by 1 year

CONCLUSIONS—The CITR shows improvement in primary efficacy and safety outcomes of islet transplantation in recipients who received transplants in 2007–2010 compared with those in 1999–2006, with fewer islet infusions and adverse events per recipient.

Diabetes Care 35:1436–1445, 2012

From 1The EMMES Corporation, Rockville, Maryland; the 2Department of Surgery, Division of Endocrinology, Diabetes and Metabolism, University of Pennsylvania, Philadelphia, Pennsylvania; the 3Department of Medicine, Division of Endocrinology/Diabetes/Metabolism, University of Miami, Miami, Florida; the 4Schultze Diabetes Institute and Department of Surgery, University of Minnesota, Minneapolis, Minnesota; the 5Islet Processing Laboratory, Institute of Biomedical Science, Baylor University Medical Center, Dallas, Texas; the 6Department of Surgery, Division of Transplant Surgery, University of Illinois at Chicago, Chicago, Illinois; the 7Department of Surgery, Division of Transplantation, University of Wisconsin, Madison, Wisconsin; the 8Department of Surgery, Division of General Surgery, Southern Illinois University, Springfield, Illinois; the 9Department of Transplant Services, University of Texas, Southwest Medical School, Dallas, Texas; the 10Department of General and Endocrine Surgery, Lille University, Lille, France; the 11Department of Surgery, Division of Transplantation and Visceral Surgery, Geneva University Hospital, Geneva, Switzerland; the 12Department of Internal Medicine, San Raffaele University, Milan, Italy; the 13Department of Medicine, Division of Endocrinology, University of Alberta, Edmonton, Alberta, Canada; the 14Department of Surgery, University of California, San Francisco, San Francisco, California; the 15Department of Medicine, Northwestern University, Chicago, Illinois; the 16Division of Diabetes, Endocrinology & Metabolism, City of Hope, Duarte, California; the 17MGH Diabetes Center, Massachusetts General Hospital, Boston, Massachusetts; the 18Department of Surgery, Division of Transplantation, Emory University, Atlanta, Georgia; the 19Department of Surgery, University of Chicago, Chicago, Illinois; the 20Centre for Transplant and Renal Research, Westmead Hospital, Westmead, New South Wales, Australia.
justifiable in carefully selected patients. Islet transplantation remains an experimental procedure in the U.S. and awaits formal results of ongoing Phase III trials to justify biologic licensure and transition to standard of care.

The Collaborative Islet Transplant Registry (CITR) has been established to monitor progress and safety of islet transplantation by using data from the U.S., Canada, and several centers in Europe and Australia supported by the Juvenile Diabetes Research Foundation (JDRF). The CITR represents the most complete collection of information on islet transplantation in the last decade. The purpose of the present inquiry is to describe trends of primary outcomes and safety profiles of islet transplantation according to cohorts defined by the year of first islet infusion (early: 1999–2002; mid: 2003–2006; or recent: 2007–2010). The analysis comprises allogeneic islet-alone and islet-after-kidney (IAK) transplants performed through 31 December 2010 with data updated through 4 January 2012.

RESEARCH DESIGN AND METHODS

Patients
The CITR is the comprehensive islet transplant registry for 27 National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK)–funded North American and JDRF-funded European and Australian centers since 1999, comprising 81% of all allogeneic islet transplants conducted as single-arm Phase II/III trials or standard of care. Patients and methods are fully described in previous and current CITR Annual Reports (3), which are publicly available. In brief, recipients of allogeneic islet transplants typically are aged between 18 and 65 years. All have had type 1 diabetes for >5 years, and >95% had documented negative fasting C-peptide (<0.3 ng/mL) and very problematic diabetes control, including hypoglycemia unawareness complicated by episodes of severe hypoglycemia and/or marked glycemic lability characterized by wide swings of blood glucose levels, often with consistently elevated HbA1c levels (>8%). This report includes no cases of islet transplantation after total pancreatectomy.

The Registry collects information on the pancreas donor(s), islet processing and testing, immunosuppression and concomitant medications, severe hypoglycemic episodes, HbA1c, fasting blood glucose and C-peptide levels, daily insulin doses, vital status, islet graft dysfunction and loss, reportable adverse events graded 3, 4, and 5 according to the Terminology Criteria for Adverse Events of the Clinical Islet Transplantation Consortium (CIT) (5), and serious adverse events (6). Islet recipients enrolled in CIT protocols consenting to have their data shared with the CITR are registered in the CITR and included in the CITR reports.

CIT protocols comprise a series of Phase II and Phase III clinical trials designed to test current immunosuppressive strategies and management practices and pursue licensure for clinical islet transplantation in the U.S. The CIT data are coordinated by the University of Iowa Clinical Trials and Data Management Center, William Clarke, PhD, Director, and are made available to the CITR through collaborative agreements via the common sponsor, the U.S. NIDDK. CITR data are rigorously monitored by the Data Coordinating Center, The EMMES Corporation, Rockville, Maryland, to comply with U.S. Food and Drug Administration Part 21 Code of Federal Regulations requirements. Site participation in the Registry requires local research ethics board approval, strict assurance of patient-identifier confidentiality, and written informed consent by the islet recipients. The CITR Publications and Presentations Committee approved the manuscript.

Statistics
At preinfusion and at each scheduled follow-up visit, five coprimary end points were assessed by laboratory measurements or clinical evaluations: basal C-peptide (further divided as ≥0.3 vs. <0.3 ng/mL), including reported complete graft loss (defined as fasting C-peptide consistently undetectable with stimulated C-peptide <0.3 ng/mL by local assay without subsequent recovery to ≥0.3 ng/mL or reinfusion, also denoted as “no function”); independence from exogenous insulin for ≥14 consecutive days; HbA1c (further divided as <6.5% and/or a drop by two percentage points or more); fasting blood glucose (further divided as 60–140 vs. <60 or >140 mg/dL); and absence of severe hypoglycemia episodes (requiring assistance of another person). The scheduled times for each infusion were immediately before transplant, 7 days, 1 month, 6 months, and annually thereafter, which was reset at each subsequent infusion. Annual time points from the last of one or more infusions per recipient were used in this analysis. Except for complete graft failure, each of these outcomes can occur, relapse, and then reoccur during follow-up, although with relatively long periods of stable status; hence, they are analyzed as prevalence (percentage) at each follow-up after the last infusion. Complete graft failure cannot remit by definition; therefore, this outcome was analyzed by failure-time techniques. When direct data were missing but graft function was known to have been previously lost and not restored, insulin independence was set as dependent and C-peptide was set at 0. Otherwise, missing data were omitted (i.e., treated as missing at random) in the computations and modeling.

For infusions given the same day from two to three different donors, the donor, procurement, processing, and isolation characteristics were summarized over the multiple donors (e.g., donor ages were averaged, total islet equivalents infused were summed, etc.) The information was summarized again over two to six infusion events per recipient. Trapped (embedded) islets are expressed as a percentage of total islet count in the preparation. Immunosuppression agents were noted as each given or not at each infusion and during the follow-up. Each recipient was classified into induction and maintenance combination categories as indicated in Table 1. All available recipient, donor, islet, and immunosuppression variables were used in the various analyses as possible predictors of the primary outcomes.

## Improvement in islet transplant outcomes

### Table 1—Recipient, donor, islet, and immunosuppression characteristics, based on numbers with data

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<tr>
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<td>255</td>
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<td>ITA</td>
<td>183</td>
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<td>Female sex</td>
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<td>C-peptide $\geq 0.3 \text{ ng/mL}$</td>
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<td>&lt;0.01</td>
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<td>Baseline hypoglycemia status</td>
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<td>No episodes or aware</td>
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<td>16</td>
<td>11</td>
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<td><strong>Baseline</strong></td>
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<tr>
<td>Insulin pump or $\geq 3$ insulin injections/day</td>
<td>162</td>
<td>220</td>
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<tr>
<td>IA-2 autoantibody (ICA 512, +)</td>
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<td>35</td>
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<td>GAD 65 autoantibody (GAA, +)</td>
<td>47</td>
<td>58</td>
<td>24</td>
<td>31.6</td>
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<tr>
<td>Insulin autoantibody (IAA, +)</td>
<td>64</td>
<td>104</td>
<td>30</td>
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<td>Blood pressure medication</td>
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<td>105</td>
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<td>97</td>
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<td>Peripheral neuropathy</td>
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<td>46</td>
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<tr>
<td>Class 1 panel reactive antibody (+)</td>
<td>17</td>
<td>31</td>
<td>18</td>
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<td>N</td>
<td>89</td>
<td>107</td>
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<td>73</td>
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<td>150</td>
<td>104</td>
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<td>215</td>
<td>109</td>
<td>96.5</td>
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<tr>
<td><strong>Donor given steroid</strong></td>
<td>59</td>
<td>103</td>
<td>49</td>
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<td><strong>Donor given insulin</strong></td>
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<td>128</td>
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<td>Thermolysin (+ other enzyme)</td>
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<td>Islets cultured ≥6 h</td>
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<td>Donor weight (kg)</td>
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<td>Donor BMI (kg/m²)</td>
<td>171</td>
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<td>Maximum donor glucose (mg/dL)</td>
<td>130</td>
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<td>Donor BUN (mg/dL)</td>
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<td>Donor total bilirubin (mg/dL)</td>
<td>107</td>
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<tr>
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<td>N</td>
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<tr>
<td>Hours of cold ischemia</td>
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<td>Hours of culture time (0 included)</td>
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<td>Total islet particles (final preparation, 1,000s)</td>
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<td>Embedded islets (%)</td>
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<td>34.5</td>
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<td>Purity (%)</td>
<td>140</td>
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<td>1.4</td>
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<td>β-Cells/kg recipient (1,000s)</td>
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<td>Islet viability (%)</td>
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<td>Stimulation index</td>
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<td>Total endotoxin infused/kg recipient</td>
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<td>IE-to-islet particle ratio</td>
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<td>Total DNA (µg)</td>
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<td>IE infused (1,000s)</td>
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<td>Cumulative IEs/kg recipient (1,000s)</td>
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<tr>
<td></td>
<td>N</td>
<td>%</td>
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<td>Induction at infusion 1</td>
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<tr>
<td>IL2RA only</td>
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<td>TNF-α inhibitor only</td>
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<td>5</td>
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<td>TCD+TNF-α inhibitor</td>
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<td>IL2RA+TCD</td>
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<td>IL2RA+TNF-α inhibitor</td>
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<td>17</td>
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<td>—</td>
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<td>Not yet reported</td>
<td>37</td>
<td>20.9</td>
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Continued on p. 1440
Improvement in islet transplant outcomes

Table 1—Continued

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<tr>
<td></td>
<td>N</td>
<td>%</td>
<td>N</td>
<td>%</td>
<td>N</td>
<td>%</td>
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<tr>
<td>CNI+ mTOR inhibitor</td>
<td>133</td>
<td>75.1</td>
<td>184</td>
<td>78.3</td>
<td>61</td>
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<td>CNI+ mTOR inhibitor+IMPDH inhibitor</td>
<td>6</td>
<td>3.4</td>
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<td>3.8</td>
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<td>12</td>
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<td>—</td>
<td>3</td>
<td>1.9</td>
<td>&lt;0.01</td>
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HTK, histidine-tryptophan-ketoglutarate; IE, islet equivalents; IL2RA, interleukin 2 receptor antagonist; IMPDH, inosine monophosphate dehydrogenase; PRA, panel reactive antibody; UW, University of Wisconsin. *Multiple responses are possible; the sum of categories may be greater than N.

2003–2006, 2007–2010), follow-up time after the first infusion, and other covariates on the rate (prevalence) of the desirable outcome for each primary end point. A multivariate analysis of all available recipient, donor, islet, and medical management factors on the outcomes was also conducted to see if changes in patient selection and management practices accounted for the observed differences in outcomes over the eras.

The occurrence and outcomes of clinically reportable adverse events (CRAEs), classified as unlikely, probably, or definitely related to the infusion procedure or to the immunosuppression regimen, were analyzed according to era. Each recipient was classified and tabulated according to his or her worst outcome of all infusion-related CRAEs and immunosuppression-related CRAEs during the entire period of infusions and follow-up for the recipient. Comparisons were made with Mantel-Haenszel χ².

Comparisons across eras clearly were not randomized, and sample sizes were not experimentally determined. In this registry data, nominal P values are reported without prespecified Type I error rates.

RESULTS—This analysis was based on 677 recipients of allogeneic islet transplantation who consented to the reporting of their data to the CITR, with 214 recipients in 1999–2002 (early), 255 in mid-2003–2006, and 208 in 2007–2010 (recent); 423 (62%) came from North America, and 254 (38%) were reported from the European and Australian JDRF sites. Transplants comprised islet alone in 575 (85%) and IAK or simultaneous islet kidney (IAK/SIK) transplant in 102 (15%). The CIT enrolled 46 (7%) in 2008–2010. They received 1,375 islet infusions from 1,502 donors, of which ~10% were islets from 2 to 3 donors infused on the same day, considered here as “multiple donor infusion.” Approximately 36% of the recipients received only one infusion, 44% received two, 18% received three, 1.3% received four, and one person received six infusions.

The CITR data represent 81% of all islet transplants performed in the North American and JDRF European and Australian centers between 1999 and 2010. The number of new islet allograft recipients doubled yearly between 1999 and 2002 (Fig. 1). A marked decline in activity from 2002 to 2003 reflected a saturation of then-existing protocol enrollments, combined with tempered enthusiasm for the procedure after some centers reported waning insulin independence at 2–3 years (7,8). The number of North American centers performing islet transplants continued to rise through 2005, although the annual number of islet allografts remained less than the 2002 levels. In 2007, there were fewer than half as many North American centers performing islet transplants and one-third of the total number of islet allografts performed compared with 2005 at a time when the commonly used collagenase enzyme Liberase became unavailable. A distinct resurgence in islet transplant activity occurred in 2008 with the available collagenase products and the start-up of the CIT trials.

Figure 1 also shows substantial shifts in immunosuppression strategies implemented during the 12-year period. The early and mideras were dominated by the Edmonton Protocol, which used an interleukin 2 receptor antagonist (e.g., daclizumab) for induction and a mammalian target of rapamycin (mTOR) inhibitor (e.g., sirolimus), together with a calcineurin inhibitor (CNI, e.g., tacrolimus) for maintenance immunosuppression. In the most recent era, there has been a shift to induction with a T-cell depleting (TCD) antibody, with or without an inhibitor of tumor necrosis factor-α (TNF-α; e.g., etanercept) and maintenance with an mTOR inhibitor or an inosine monophosphate dehydrogenase inhibitor (e.g., mycophenolic acid) combined with a CNI.

Table 1 summarizes the preinfusion recipient characteristics according to era. Over time, recipients with C-peptide ≥0.3 ng/mL have been excluded. Increasingly, recipients have been selected at older age and with longer type 1 diabetes duration, requiring slightly less insulin and having better kidney function, as indicated by lower serum creatinine, suggesting more appropriate patient selection. Consistent with trends in clinical practice, more were using insulin pumps for insulin delivery, which may explain the slightly lower daily insulin requirement, and more were taking lipid-lowering medications. Following national trends, donor weight increased, and consistent with trends in critical care medicine, more donors received insulin with a consequent decrease in donor glucose. Donor HbA1c, when sampled, remained within normal levels in all eras. There were also definite shifts in preservation method and collagenase type, and more islet preparations were cultured. The clinical effects of procurement, processing, and final islet characteristics are the focus of a separate analysis. Recent years have seen a substantial decline in the use of daclizumab, with a substantial rise in polyclonal T-cell–depleting antibodies and/or etanercept, as well as notable declines in sirolimus use, with increased use of mycophenolic acid.

There were increasing levels of missing data with longer follow-up, which is a mixture of data unavailable from the medical record and data still pending entry into the registry. The percentages of missing data for insulin independence were 3% at 1 year, 5% at 3 years, and 7% at 5 years and for other primary end points were 10 to 20% over years 1–3.
Of those who received transplants in the 1999–2002 era, 51% were insulin-independent at 1-year after the first infusion, regardless of reinfusion, and this declined to 36% at 2 years and to 27% at 3 years. By contrast in the 2007–2010 era, 66% were insulin-independent at 1 year, 55% at 2 years, and 44% at 3 years ($P = 0.01$, Fig. 2A). The decline in the rate of insulin independence during 5 years of follow-up in all eras is significant ($P < 0.001$). The difference in this decline among the three eras ($P = 0.006$ for years-by-era) indicates that the rate of decline is less steep, showing notable improvement in durability in the most recent era. Durability of islet graft function, as measured by fasting C-peptide $\geq 0.3$ ng/mL, improved significantly over the eras ($P < 0.001$, Fig. 2B, left). The rate of graft function loss was significantly reduced if insulin independence was previously achieved, an effect seen in all eras (Fig. 2B, right). Nearly all islet recipients had significant improvements in $\text{HbA}_1c$ and fasting blood glucose after islet transplantation. The composite end point of $\text{HbA}_1c < 6.5\%$ or a drop by two or more percentage points shows improvement from the early era to the mid era ($P = 0.03$), although no further improvement in the most recent era, with 2–5-year success rates of 50–60% in the recent era (Fig. 2C, left). Fasting blood glucose showed a marked improvement from the early to mid eras ($P < 0.01$, not shown).

Severe hypoglycemia was prevalent at first infusion in $>90\%$ of all subjects in all eras. Available data on severe hypoglycemic events, regardless of previous graft loss (C-peptide $<0.3$ ng/mL without recovery), shows $>90\%$ remained free of severe hypoglycemic events in all eras, and this relationship persisted through 5 years of follow-up (Fig. 2C, right). Any differences by era on resolution of severe hypoglycemic events were neither detectable nor important relative to this sustained, high level of benefit. If data on severe hypoglycemic events were missing and previous complete graft loss was counted as return to severe hypoglycemic events—an extreme assumption—there was still improvement in 2003–2006 compared with 1999–2002 at years 2–4 ($P = 0.03$, not shown).

Concurrent C-peptide is a strong correlate of all the other primary outcomes: the higher the C-peptide, the greater the likelihood of $\text{HbA}_1c < 6.5\%$ or a drop by two percentage points ($P < 0.001$; Fig. 2D), the greater the likelihood of absence of severe hypoglycemic events ($P < 0.001$; Fig. 2D), the greater the likelihood of fasting blood glucose in the 60–140 mg/dL range ($P < 0.001$, not shown), and the greater the likelihood of insulin independence ($P < 0.001$, not shown).

A comprehensive model of all predictive factors—noting the shifts in patient age and immunosuppression strategies over the eras (Table 1)—largely accounted for the differences by era in insulin independence (Table 2). The effect of T-cell-depleting agents in conjunction with TNF-$\alpha$ inhibitors shows on enduring insulin independence (9) is confirmed: 50–62% of recipients receiving this induction regimen were insulin-independent at years 3–5 after the last infusion (Fig. 2A, right), compared with 34–43% for those not receiving TCD+TNF-$\alpha$ inhibitors.

Reinfusion is performed when the first graft loses function completely or declining function is proven by declining C-peptide levels. Islet reinfusion has decreased substantially during the 12-year period: 48%
of recipients were reinfused by 1 year in 2007–2010 vs. 60–65% in 1999–2006 (P = 0.01).

Mortality is low in this group of type 1 diabetic individuals with substantial disease burden, with stable event rates during the 12-year period (Fig. 3A). The incidence of life-threatening events has declined (P = 0.02; Fig. 3B). The incidence of any CRAE in year 1 declined from 50 to 53% in 1999–2006 and to 38% in 2007–2010 (P = 0.02; Fig. 3C).

Peritoneal hemorrhage or gallbladder perforation declined from 5.4% in 1999–2003 to 3.1% in 2007–2010. The Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) calculated glomerular filtration rate (GFR) declined after islet

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**Figure 2**—A: Rates of insulin independence after allogeneic islet infusion (islet transplant alone and IA), annually after last infusion. Left: By era (P = 0.02). Right: By induction immunosuppression category (P < 0.01). B: Durability of graft function (basal C-peptide ≥0.3 ng/mL) after the last infusion, by era (P < 0.001; left). The immediate drop at time 0 is occurrences of primary nonfunction (i.e., C-peptide never ≥0.3 ng/mL). In the most recent era, 95% of those who ever achieved insulin independence (II) retained graft function through 3 years after last infusion compared with 70% for those who never achieved II (P < 0.001; right). C: Percentage of patients with HbA1c <6.5% or drop by two percentage points (P = 0.03; left); and absence of severe hypoglycemic events regardless of complete graft failure (P = NS by era; there were insufficient data from 2007–2010; right). D: The percentage with HbA1c <6.5% or drop by 2% increases with increasing C-peptide level (P < 0.001; left), as does absence of severe hypoglycemic events (P < 0.001; right), annually after the last infusion. (A high-quality color representation of this figure is available in the online issue.)
transplantation (Fig. 3D); however, there are no published comparable follow-up data in similar groups of type 1 diabetes. No primary efficacy or safety end points were associated with recipient or donor sex or ethnicity.

CONCLUSIONS—In North America, the number of centers performing clinical islet transplants and the total number of islet transplants declined in 2006–2007, with a distinct resurgence in 2008. The reasons for the decline are not directly captured by the Registry but likely reflect changes in the production and availability of the collagenase enzymes used for islet digestion, tempered enthusiasm with respect to long-term clinical outcomes of insulin independence (7,8,10), concern for effect of immunosuppression on kidney function in islet-alone recipients (11,12), concern for risk of sensitization to donor HLA (13–15), and saturation of the referral base for patients with the severest forms of unstable type 1 diabetes. However, with the start of the new CIT protocols in 2008, coupled with more encouraging recent trends in longer-term outcomes with novel protocols using T-cell depletion for induction (16,17), the number of new islet cell recipients has increased annually in the most recent era.

Direct evidence is presented of the importance of durable islet graft function to achieve multiple clinical benefits as a consequent effect. Positive C-peptide is strongly associated with all of the other primary clinical outcomes; hence, the factors that drive positive C-peptide necessarily lead to the other clinical benefits, although additional factors may also contribute to the other benefits. A comprehensive analysis of the effect of all available factors on these primary co-outcomes indicates that older recipient age, lower initial insulin requirement, and the use of T-cell depletion, particularly when given in conjunction with TNF-α inhibitors, are significantly associated with improved clinical outcomes. The numbers are too low to definitively assess the impact of a shift in maintenance immunosuppression, with mycophenolic acid replacing mTOR inhibitors, and both agents are still usually administered in combination with a CNI.

It must be noted that the CITR data have not been accruing in real time; rather, as sites have joined over the 12-year life of the Registry, large portions of the data, including some of the historical data, have been reported during the last 1–3 years. Hence, the current results may vary somewhat from previously published reports, including the CITR Annual Reports. The present data are the most comprehensive and up-to-date information available for the 12-year period 1999–2010.

In the present analysis, the increasing levels of missing data with increasing follow-up time pose some limitation. Strengths of the analysis are the most complete available set of data and ability to track trends during this 12-year period of steroid-free immunosuppression. Stratifying the CITR data by era of transplant shows a compelling trend toward better outcomes in the recent era (P ≤ 0.01), despite the still relatively low total number of islet transplant recipients worldwide. There is an indication of moving toward selection of older recipients with longer-standing diabetes and absence of C-peptide to tip the risk-to-benefit ratio in their favor. The trend toward heavier donors is likely due to donor availability in the midst of a global obesity epidemic and possibly to the known association between higher donor weights and the higher number of islet equivalents isolated (18). This must be balanced against the detrimental effects of transplanting islets derived from donors with unsuspected type 2 diabetes (19), and for this reason, it is important to confirm that the HbA1c of an obese donor is within the normal range before transplantation.

In the past, transplanting islets rapidly after isolation was believed to be optimal. In recent years, the preference toward transplanting islets after a short culture period emphasizes the current supposition that cultivating removes the nonviable islets and decreases tissue factor expression that can lead to nonspecific inflammation and islet loss after transplant (20). The percutaneous infusion technique occasionally resulted in intraperitoneal hemorrhage and portal branch vein thrombosis early on; however, these complications have occurred less often in the present era.

Whole pancreas transplantation is an approved option for β-cell replacement in type 1 diabetes, although it is mostly limited to patients simultaneously receiving a kidney transplant for diabetic nephropathy and often excludes older patients and those with coronary artery disease due to the potential for significant surgical morbidity. Thus, islet transplantation may offer a complementary alternative to whole pancreas transplantation in patients who are not candidates for or are unwilling to accept the risks of major surgery, and so some estimation of comparative efficacy is required. In the 2007–2010 era, islet graft survival (C-peptide ≥0.3 ng/mL) of 92% at 1 year and 83% at 3 years (Fig. 2B) compares very favorably with whole pancreas graft survival of 80% at 1 year and 61% at 3 years (21). In the recent era, these graft survival rates translate to an unconditional 44% insulin independence at 3 years (Fig. 2A), the highest long-term islet transplant success rate observed to date. Although this is still short of the 61% insulin independence reported in the most successful cohort of type 1 diabetes pancreas-alone transplant recipients (22), this difference may be explained by the transplantation of 100% of a normal islet β-cell mass with a whole pancreas compared with a variable islet β-cell mass surviving the engrafment of isolated islets and resulting in a reduced β-cell secretory capacity (23). In addition, throughout the 12-year period, these data show an enduring benefit in HbA1c reduction and stabilization of fasting blood glucose.

Importantly, the presence of insulin-dependent islet graft survival defined by C-peptide >0.3 ng/mL confers protection from severe hypoglycemia, and this effect persists even after the islet graft is lost. This declining rate of islet graft loss by era suggests that more recent strategies of immunosuppression, as identified in the multivariate analysis, may better protect islets from alloimmune rejection and recurrent autoimmunity. The successful strategies have all included CNIs that are known to exhibit β-cell toxicity at high doses; however, one study showed modern use of lower-dose, CNI-based

### Table 2—Factors predictive of insulin independence after last infusion

<table>
<thead>
<tr>
<th>Results from generalized estimating equations</th>
<th>Odds ratio (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total infusions</td>
<td>1.44 (1.06–1.98)</td>
<td>0.02</td>
</tr>
<tr>
<td>Recipient age (each additional year)</td>
<td>1.04 (1.02–1.07)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Islets cultured ≥6 h</td>
<td>1.82 (1.06–3.15)</td>
<td>0.03</td>
</tr>
<tr>
<td>Stimulation index ≥1.5</td>
<td>1.83 (1.23–2.72)</td>
<td>0.05</td>
</tr>
<tr>
<td>T-cell depletion + TNF-α inhibitor</td>
<td>2.38 (0.95–5.94)</td>
<td>0.06</td>
</tr>
</tbody>
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Immunosuppression resulted in a 100% normal β-cell secretory capacity in whole pancreas transplant recipients (23), supporting that these agents can be used and may even be necessary for successful islet transplantation. Finally, the finding that the rate of graft function loss was significantly reduced when insulin independence was previously achieved suggests that the engraftment of a sufficient islet β-cell mass to eliminate the need for exogenous insulin may mitigate nonimmunologic islet graft loss believed to occur in the setting of increased β-cell demand. Present strategies to improve the proportion of islets surviving engraftment are expected to lead to improved functional outcomes for islet recipients (24).

The CITR shows consistent trends toward improved primary outcomes of islet transplantation in the cohort who received transplants in 2007–2010 compared with those in 1999–2006. Islet transplantation currently offers substantial protection from severe hypoglycemic episodes and high rates of freedom from exogenous insulin requirements in a minimally invasive setting. Emerging innovations in islet production, processing, delivery, and immunosuppressive protection undoubtedly will advance the field. Islet transplantation has already moved from Phase I/II to Phase III evaluation, with the results from the CIT eagerly awaited to provide efficacy and safety information for a standardized...
approach to islet isolation and immunosuppression management.

Acknowledgments—The CITR is funded by the NIDDK, National Institutes of Health, and by a supplemental grant from the JDRF International. Additional data were made available through cooperative agreements with the U.S. United Network for Organ Sharing, Alexandria, Virginia, the Administrative and Bioinformatics Coordinating Center of the City of Hope, Duarte, California (1999–2009), and the NIDDK-sponsored CIT (www.citregistry.org), coordinated by the University of Iowa Clinical Trials and Data Management Center (2008–present).

No potential conflicts of interest relevant to this article were reported.

F.B.B. was the principal investigator of the Registry. M.R.R., R.A., J.O., and P.A.S. contributed substantially to the analysis of the data and interpretation of the results, assumed responsibility for clinical data reported to the Registry, and reviewed and edited the manuscript. B.J.H., B.N., J.S.O., M.R.G., F.P., T.B., and A.M.J.S. contributed substantially to the analysis of the data and interpretation of the results and assumed responsibility for clinical data reported to the Registry. S.W. was the study manager of the Registry. M.L., A.P., X.L., F.K., N.A.T., P.W., P.J.O., K.L.B., M.J.A., C.L., T.W.H.K., L.A.F., and M.B. assumed responsibility for clinical data reported to the Registry and reviewed and edited the manuscript. A.S., P.M., D.B.K., P.G.S., E.C., A.N., C.G., Y.C.K., and M.-C.V. assumed responsibility for clinical data reported to the Registry. S.M. contributed to the analysis of the data and reviewed and edited the manuscript. F.B.B. and S.W. are the guarantors of this report.


Parts of this study were presented at the 72nd Scientific Sessions of the American Diabetes Association, Philadelphia, Pennsylvania, 8–12 June 2012.

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