

Long-Term Follow-Up of the Edmonton Protocol of Islet Transplantation in the United States

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We report the long-term follow-up of the efficacy and safety of islet transplantation in seven type 1 diabetic subjects from the United States enrolled in the multicenter international Edmonton Protocol who had persistent islet function after completion of the Edmonton Protocol. Subjects were followed up to 12 years with serial testing for sustained islet allograft function as measured by C-peptide. All seven subjects demonstrated continued islet function longer than a decade from the time of first islet transplantation. One subject remained insulin independent without the need for diabetic medications or supplemental transplants. One subject who was insulin-independent for over 8 years experienced graft failure 10.9 years after the first islet transplant. The remaining six subjects demonstrated continued islet function upon trial completion, although three had received a supplemental islet transplant each. At trial completion, five subjects were receiving insulin and two remained insulin independent, although one was treated with liraglutide. The median hemoglobin A_{1c} was 6.3% (45 mmol/mol). All subjects experienced progressive decline in the C-peptide/glucose ratio. No patients experienced severe hypoglycemia, opportunistic infection, or lymphoma. Thus, although the rate and duration of insulin independence was low, the Edmonton Protocol was safe in the long term. Alternative approaches to islet transplantation are under investigation.

Abbreviations: CITR, Collaborative Islet Transplant Registry; DPP-4, dipeptidyl peptidase-4; DSA, donor-specific antibody; GAD65, glutamate decarboxylase 65;

GLP-1, glucagon-like peptide-1; HbA_{1c}, hemoglobin A_{1c}; IEQ, islet equivalent; MMTT, mixed meal tolerance test; PML, progressive multifocal leukoencephalopathy; PTLD, posttransplant lymphoproliferative disorder

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Introduction

A subgroup of type 1 diabetes mellitus patients are severely disabled by refractory hypoglycemia with unawareness, despite improved care and treatment. In the last decade, substantial progress has been made in the field of islet transplantation. In 2001, the multicenter NIS01/ITN005CT (NIS01) protocol explored the feasibility and reproducibility of the methods used in the previously conducted “Edmonton Protocol” to evaluate islet transplantation together with a steroid-free immunosuppression (IS) regimen (1,2). Protocol NIS01 enrolled 36 subjects with stimulated C-peptide levels <0.3 ng/mL who were followed for 7 years posttransplantation through August 2010.

Although immunosuppression is required to maintain islet graft function, it is not covered by United States health insurers because administration of islet grafts for treatment of type 1 diabetes mellitus has been considered experimental. The purpose of the ITN040CT (EXIIST-Extended Immunosuppression in Islet Transplantation) protocol was to provide immunosuppression to eliminate the financial barrier of long-term immunosuppression and further evaluate the long-term efficacy and safety of islet transplantation from patients enrolled in the Edmonton Protocol by continuing to provide immunosuppressive medication for U.S. islet transplant recipients of protocol NIS01 who demonstrated persistent graft function as measured by C-peptide production at the completion of the NIS01 Edmonton trial.

Research Design and Methods

Subjects who participated in the NIS01 protocol at U.S. sites and met eligibility criteria for EXIIST (NCT 01309022) were enrolled starting in August 2010 and were followed with yearly visits until study closure on April 17, 2014. This trial is registered on ClinicalTrials.gov as NCT01309022. (The former or underlying trial [ITN005CT] was NCT00014911.) Details of this trial can be found at <https://clinicaltrials.gov/ct2/show/NCT01309022?>

term=Immunosuppressive+Medications+for+Participants+in+ITN005CT&rank=1.

Initially, protocol NIS01 followed subjects for 3 years after the first islet transplant. It was extended to follow subjects for a total of 7 years after last transplantation. Three subjects received one additional islet transplant in a different clinical trial upon completion of the originally planned 3-year follow-up of NIS01 (3). These subjects were also enrolled in the NIS01 extended follow-up when the extension phase became available.

These subjects were subsequently enrolled in EXIIST to increase the number of patients followed long term to determine efficacy and safety of the long-term immunosuppression particularly on the incidence of infection, malignancy, and renal insufficiency. The planned immunosuppressive regimen in NIS01 was sirolimus and tacrolimus. However, six of the seven subjects discontinued sirolimus, five due to mouth ulcers and one due to ischemic colitis. The subjects were switched to mycophenolate mofetil or mycophenolic acid.

The EXIIST inclusion criteria included the following: previous participation in protocol NIS01; peak C-peptide >0.3 ng/mL during a mixed meal tolerance test (MMTT) within 12 months of study screening; IS consisting of any combination of calcineurin inhibitors, antimetabolites, and antiproliferative drugs; and transplanted at a U.S. site.

The EXIIST exclusion criteria included the following: serum creatinine >1.6 mg/dL; insulin requirement >1.0 IU/kg/day; hemoglobin A_{1c} (HbA_{1c}) >12% (108 mmol/mol); and severe hypoglycemia defined as the absence of adequate autonomic symptoms at plasma glucose levels of <54 mg/dL requiring treatment with glucagon, outside assistance, or treatment in an emergency room or hospital within a 12-month period.

Ethical approval for the study was provided by the sites' Institutional Review Boards. This study was designed and performed according to current Good Clinical Practices and the applicable local regulatory requirements for participating institutions.

EXIIST study endpoints

The primary endpoint was the duration of sustained islet allograft function as defined by C-peptide >0.3 ng/mL at 90 min in response to a MMTT. Additional endpoints included 90-min C-peptide levels, adverse events, and selected laboratory parameters measured at study visits. Collection of adverse events was limited to cirrhosis, malignancies, hypoglycemia, serious adverse events, or stage three adverse events related to study participation or higher as defined by the National Cancer Institute Common Terminology Criteria for Adverse Events Version 4.0, can be found at http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_8.5x11.pdf and stage three or higher renal insufficiency or as defined by the Kidney Disease Outcomes Quality Initiative (4).

Sample size

Sample size was based on the number of eligible NIS01 subjects. Seven subjects were in the extended follow-up portion of the NIS01 trial and all elected to enroll in EXIIST. The remaining 12 U.S. subjects exited the NIS01 trial prior to the extended follow-up as shown in Figure 1.

Statistical analysis

The C-peptide-to-glucose ratio was calculated to explore the change in both parameters over time to monitor beta-cell mass and assess islet graft function (5).

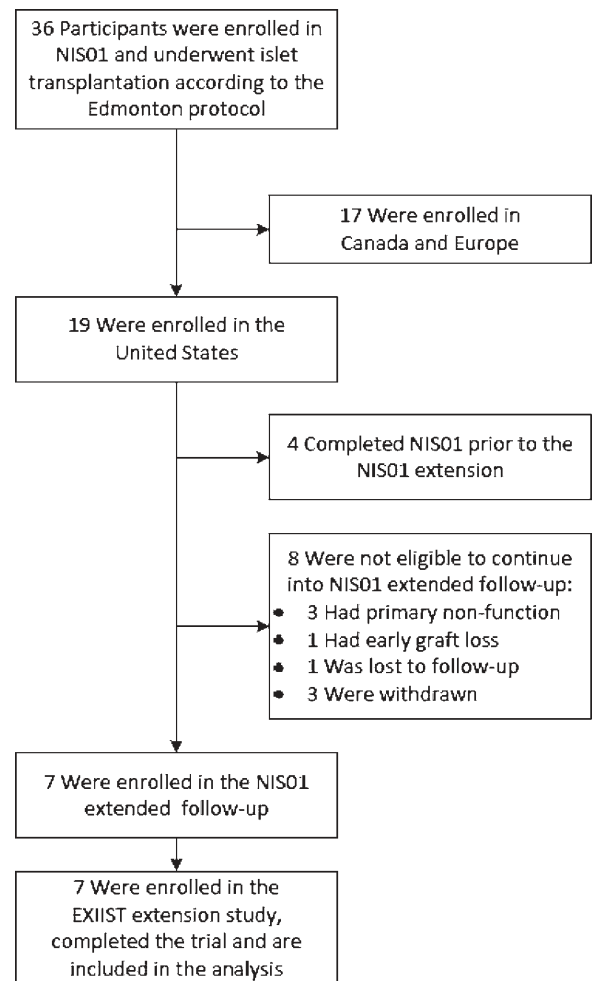


Figure 1: Subject disposition for NIS01 and EXIIST. Primary nonfunction was defined as an initial C-peptide level of <0.3 ng/mL. Early graft loss was defined as an initial increase in the C-peptide level but a decrease to <0.3 ng/mL within 2 months. One U.S. site closed prior to the addition of extended follow-up to NIS01 since all subjects had completed the initial follow-up. All four subjects had detectable C-peptide (90-min C-peptide >1.3 ng/mL) and were on insulin at the time of study completion. EXIIST, Extended Immunosuppression in Islet Transplantation.

During protocol NIS01, data on insulin use were collected yearly; the exact start and stop dates of insulin use for the subjects were not collected. Therefore, all insulin-independence duration calculations are based on study visit dates rather than actual insulin stopping and starting dates.

P-values for change over time were calculated using the signed-rank test. Over the duration of the EXIIST study, all subjects had five visits. To account for the repeated measurements nested within subjects, correlations between two continuous variables were estimated using a mixed-model approach (6).

To account for the nesting of data in the evaluation of the impact of the C-peptide-to-glucose ratio and C-peptide (90-min and fasting) on insulin independence, a logistic regression model was fit using a generalized

estimating equation with an exchangeable covariance structure. Because only seven subjects contributed to the analysis, p-values were computed using both a small sample adjustment to the Wald chi-square statistic (7) and a score statistic. Results for the score statistic were more conservative and are presented here.

All analyses were conducted using Statistical Analysis Software, SAS version 9.3 (SAS Institute Inc., Cary, NC). Datasets for these analyses are accessible through TrialShare, a public website managed by the Immune Tolerance Network (<https://www.itntrials.org/EXIIST.url>).

Results

Study subjects

Between August and November 2010, seven subjects were enrolled in EXIIST at three U.S. sites. Prior to entering EXIIST, each of the seven subjects received up to three islet infusions with a total of 20 infusions (median 3) performed (median total islet equivalent [IEQ] 1.1×10^6 and median total IEQ/kg 18 721). The median follow-up of all seven patients was 10.2 years (range, 8.1–10.6 years) from the time of last islet transplantation to the closure of EXIIST. Table 1 shows subjects’ demographic characteristics, selected laboratory parameters, and insulin use prior to any islet transplantations and at the last visit in 2014. Table 2 shows detailed information on the islet transplants.

All subjects demonstrated islet graft function for at least 10 years (see below). Six of the seven subjects demonstrated continued islet graft function, as defined by the primary endpoint, through their last follow-up visit (Table 1 and Figure 2). The follow-up time for these six subjects was censored at their last follow-up visit. Median follow-up in these six subjects was 11.6 years (range 11.2–12.0 years) from first transplant and 9.2 years (range, 8.1–10.6 years) from last transplant.

The median 90-min C-peptide value in response to a MMTT for the six subjects with functioning grafts was 4.5 ng/mL (range 2.6–6.6 ng/mL), the median 90-min glucose value was 203 mg/dL (range 85–256 mg/dL), and the median 90-min C-peptide-to-glucose ratio value ($\times 100$) was 2.4 (range 1.0–6.8) at the last study visit. For all seven subjects, the median 90-min C-peptide value was 4.4 ng/mL (range <0.1 –6.6 ng/mL), the median 90-min glucose value was 239 mg/dL (range 85–267 mg/dL), and the median 90-min C-peptide-to-glucose ratio was 1.8 (range 0.0–6.8) at the last study visit.

During the EXIIST study, subjects exhibited a progressive decrease in C-peptide levels (median change -1.9 ng/mL) and in C-peptide-to-glucose ratio (median change -1.1) during the duration of follow-up (Figures 3 and 4, and Figure S1).

All seven subjects achieved insulin independence after their last islet transplant for a median time of 54 months

Table 1: Demographic and clinical characteristics at pretransplant baseline and last study visit

NIS01 Subject ¹	Sex	Race	Age (years)		Weight (kg)		BMI (kg/m ²)		Blood pressure (mm Hg)		HbA _{1c} (%)		HbA _{1c} (mmol/mol)		90 min C-peptide (ng/mL)		Creatinine (mg/dL)		Insulin (U/kg/day)	
			Pre	Last	Pre	Last	Pre	Last	Pre	Last	Pre	Last	Pre	Last	Pre	Last	Pre	Last	Pre	Last
1	Female	White	48	60	59.3	52.2	21.0	18.6	132/70	116/74	6.9	6.7	52	50	0.12	4.60	0.9	1.5	0.74	0.38
18 ²	Female	White	34	46	60.0	60.3	23.0	22.8	120/80	113/72	6.4	6.9	46	52	0.10	3.41	0.8	0.6	0.50	0.25
19 ³	Male	White	47	59	72.7	79.0	24.0	25.7	135/80	117/73	6.2	6.2	44	44	0.10	2.55	0.8	1.0	0.62	0.15
20 ^{2,4}	Female	White	50	62	61.7	56.5	20.1	18.4	110/60	112/66	7.8	5.7	62	39	0.10	5.78	0.9	0.8	0.29	0
29 ³	Female	White	35	47	57.0	46.4	24.0	19.6	122/78	95/55	6.8	6.4	51	46	0.10	4.41	0.8	0.84	0.49	0.17
33	Female	White	30	41	66.2	67.3	22.9	23.2	121/66	122/73	8.0	6.7	64	50	0.11	<0.1	0.7	0.84	0.45	0.39
35 ⁴	Male	White	45	56	70.4	63.7	24.9	22.6	115/65	147/79	7.0	6.1	53	43	0.11	6.60	1.0	1.04	0.45	0

Pre-assessments occurred prior to islet transplantation on NIS01. Last assessments occurred during the last EXIIST visit.

EXIIST, Extended Immunosuppression in Islet Transplantation; HbA_{1c}, hemoglobin A_{1c}.

¹Subject IDs are those used in the NIS01 publication (2).

²Subject was on the non-insulin diabetic medication linagliptin.

³Subject was on the noninsulin diabetic medication liraglutide.

⁴Subject 35 received all transplants during the NIS01 protocol while subject 20 received an additional islet transplant outside of the NIS01 trial; both remain insulin independent.

Table 2: Islet transplant data

NIS01 subject ¹	NIS01 transplant data			Transplant outside of NIS01			Total transplant data			
	No. transplants NIS01	Total NIS01 IEQ × 10 ⁶	Total IEQ/kg	Years of transplants	Total IEQ × 10 ⁶ addt.	Total IEQ/kg	Year of transplant	Total no. of transplants	Total IEQ × 10 ⁶	Total IEQ/kg
1	3	1.11	18721	2002–2003	–	–	–	3	1.11	18 721
18	2	0.80	13912	2002	0.38	7150	2006	3 ²	1.18	21 062
19	2	0.85	11789	2002	0.37	5268	2006	3 ²	1.22	17 057
20	1	0.47	7682	2002	0.41	6868	2006	2 ²	0.88	14 550
29	3	1.04	20261	2002–2004	–	–	–	3	1.04	20 261
33	3	1.01	15526	2002–2003	–	–	–	3	1.01	15 526
35	3	1.32	19745	2002–2003	–	–	–	3	1.32	19 745

¹Subject IDs are those used in the NIS01 publication (2).

²Subject received an islet transplant outside of the NIS01 trial.

(range 5–126 months) (Figure 3). Four subjects were insulin independent at the beginning of the EXIIST trial; two of these four received supplemental islet transplants.

Two of the seven subjects remained insulin independent at their last follow-up visit. Subject 35 (Table 1) has been insulin independent for 126 months, 10.5 years. The subject was receiving 0.45 units (U)/kg (32 U) of insulin per day prior to transplantation, received three transplants (total IEQ 1.32×10^6 and IEQ/kg 19 745), and has an HbA_{1c} of 6.1% (43 mmol/mol). Subject 20 (Table 1), has been insulin independent for 67 months, 5.6 years. The subject was receiving 0.29 U/kg (18 U) of insulin per day prior to transplantation, received two transplants (total IEQ 0.88×10^6 and IEQ/kg 14 550), has an HbA_{1c} of 5.7% (39 mmol/mol), and was taking linagliptin at the last follow-up visit. Prior to the first islet transplant, both subjects were on ≤ 0.45 U/kg/day of insulin, which was less than the dose being received by four of the five other subjects.

Four of the seven subjects had functional grafts but were not insulin independent at their last visit. At 11 years posttransplantation, insulin use in U/day was less than at pretransplant, despite loss of insulin independence. At the last visit, these four subjects were receiving 24%, 35%, 50%, and 51% of their pretransplant insulin amount.

One of the seven subjects, Subject 33 (Table 1), was insulin independent for 8.5 years, but experienced graft failure with loss of detectable C-peptide 10.9 years after the first transplant and 10.2 years after the last transplant. This subject received three transplants with a total IEQ of 1.01×10^6 (IEQ/kg 15 526) under NIS01 and was receiving tacrolimus and mycophenolate mofetil at the last assessment. At the time of graft failure, donor-specific antibodies (DSAs) to HLA major histocompatibility Class I and II antigens were not present and glutamate decarboxylase 65 (GAD65) antibodies were 0.02 nmol/L (expected ≤ 0.02 nmol/L). At the last visit, this subject was also on less insulin (87% of pretransplant) and the HbA_{1c} decreased from 8% (64 mmol/mol) pretransplantation to 6.7% (50 mmol/mol).

During the EXIIST trial, no statistically significant correlations were observed between 90-min C-peptide levels and glucose levels (both fasting and 90-min MMTT) or insulin dosage. In addition, no statistically significant correlations were observed between insulin dosage and either basal C-peptide levels or glucose levels (both fasting and 90-min MMTT). There was also no statistically significant correlation between the total IEQ transplanted and either insulin independence or graft failure at the conclusion of the EXIIST trial.

In logistic models to identify variables associated with insulin independence, the C-peptide-to-glucose ratio was the single most important variable (p-value 0.04). Based on

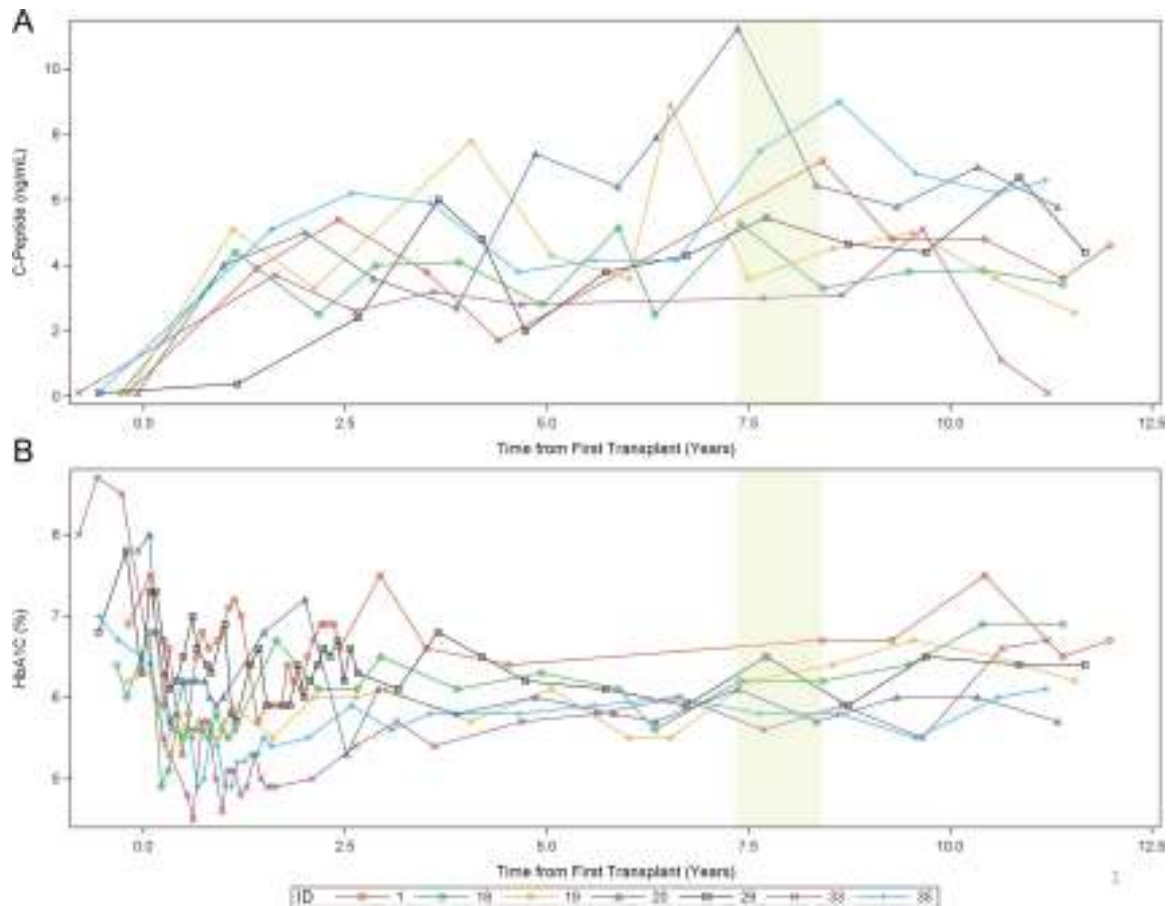


Figure 2: Ninety-minute C-peptide (A) and HbA_{1c} (B) over time by subject. The band represents the switch from the NIS01/ITN005CT study to the ITN040CT study. HbA_{1c}, hemoglobin A_{1c}.

our model, higher C-peptide-to-glucose ratios increase the probability of insulin independence.

The median HbA_{1c} percentage values tended to be lower at the last visit (6.4% (46 mmol/mol) [range 5.7–6.9% (39–52 mmol/mol)]) compared to values pretransplantation (6.9% (52 mmol/mol) [range 6.2–8.0% (44–64 mmol/mol)]), but these were not statistically significant ($p=0.16$). This included the subject with late islet graft failure as described above. The HbA_{1c} levels for all subjects remained relatively stable over time unless there was loss of islet function (Figure 2). At the end of the trial, four subjects had HbA_{1c} values <6.5% (48 mmol/mol) and all seven had values <7% (53 mmol/mol), two of whom were insulin independent.

Adverse events

The trial was generally safe overall. No episodes of opportunistic infection, posttransplant lymphoproliferative disorder (PTLD), progressive multifocal leukoencephalopathy (PML) or severe hypoglycemia were observed during

the conduct of the EXIIST trial. There was no progression of diabetic retinopathy or new onset of diabetic retinopathy. No stage 3 neuropathy occurred. One subject experienced basal and squamous cell carcinomas of the skin, possibly related. Another subject experienced possibly related gastroenteritis and two hyperglycemia events. No other related adverse events were observed.

As shown in Table 1, no subjects experienced substantial weight gain or decline in renal function. One subject, number 1, experienced sustained elevated creatinine levels of 1.5 mg/dL starting approximately 2 years after the first islet transplant that did not worsen over the course of the EXIIST trial. From the time of first transplant to the end of the study follow-up, one subject experienced an increase in systolic blood pressure to >130 mmHg. At the last study visit, two subjects had diastolic blood pressures of <70 mmHg; one subject was <70 mmHg prior to transplant and the other was >70 mmHg. Two additional subjects had diastolic blood pressures of <70 mmHg prior to their first transplant and experienced increases to 70–80 mmHg by the end of study follow-up.

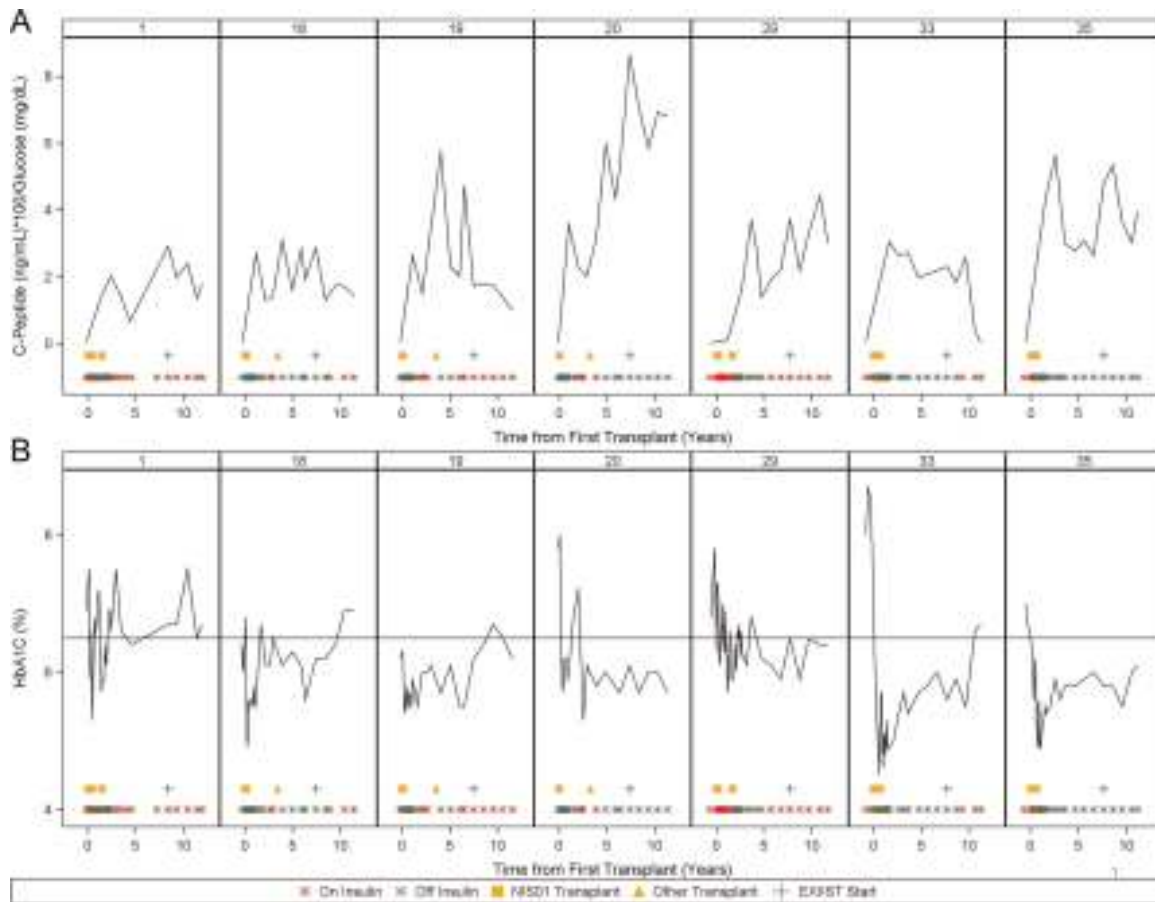


Figure 3: C-peptide to glucose ratio (A) and HbA_{1c} (B) over time for each subject with insulin use information, timing of transplants, and ITN040CT study start date. The reference line is drawn at the HbA_{1c} value of 6.5%. HbA_{1c}, hemoglobin A_{1c}.

Immunosuppressive medications were maintained per institutional standards. All seven subjects received tacrolimus (median trough concentration was 5.6 ng/mL with values ranging from 1.4 to 10.6 ng/mL during EXIST; Figure S2). The sirolimus trough level range for the one subject who continued receiving drug was 4.9–13.3 ng/mL during the EXIST trial. Four of the seven subjects were also taking a medication for diabetes control at the final study visit; two subjects were taking the incretin mimetic liraglutide (Victoza[®], Novo Nordisk, Bagsværd, Denmark), and two were taking the dipeptidyl peptidase-4 (DPP-4) inhibitor linagliptin (Tradjenta[®], Boehringer Ingelheim, Inc., Ridgefield, CT). Three subjects were on glucagon-like peptide-1 (GLP-1) based therapy at the time of their last transplant (subjects 18, 19, and 20) and one (subject 29) started therapy 2 years after their last transplant.

Discussion

The major strengths of the EXIST trial are that it was multicenter and evaluated the long-term safety and efficacy of islet transplantation in type 1 diabetes mellitus subjects

in the United States through long-term detailed observations over 10 years. There were no deaths, PTLD, PML, serious infections, or episodes of severe hypoglycemia even with exposure to long-term broad immunosuppression. Superficial squamous/basal cell carcinoma was the only malignancy reported in one subject. All subjects experienced stable renal function during the EXIST trial. One subject was enrolled with and continued with renal insufficiency but creatinine values were stable over the course of the trial.

No weight gain was observed. Systolic blood pressure levels did not increase substantially and renal function did not deteriorate despite nearly a decade of exposure to immunosuppression with calcineurin inhibitors or mTOR inhibitors. Diastolic blood pressure values of <70 mmHg have been associated with increased cardiovascular mortality and arterial stiffness (8,9). In two of three subjects with diastolic blood pressure <70 mmHg prior to transplant, increased diastolic blood pressure was reported, possibly improving future cardiovascular outcomes. Blood pressure assessments, however, were only obtained at the yearly follow-up visits.

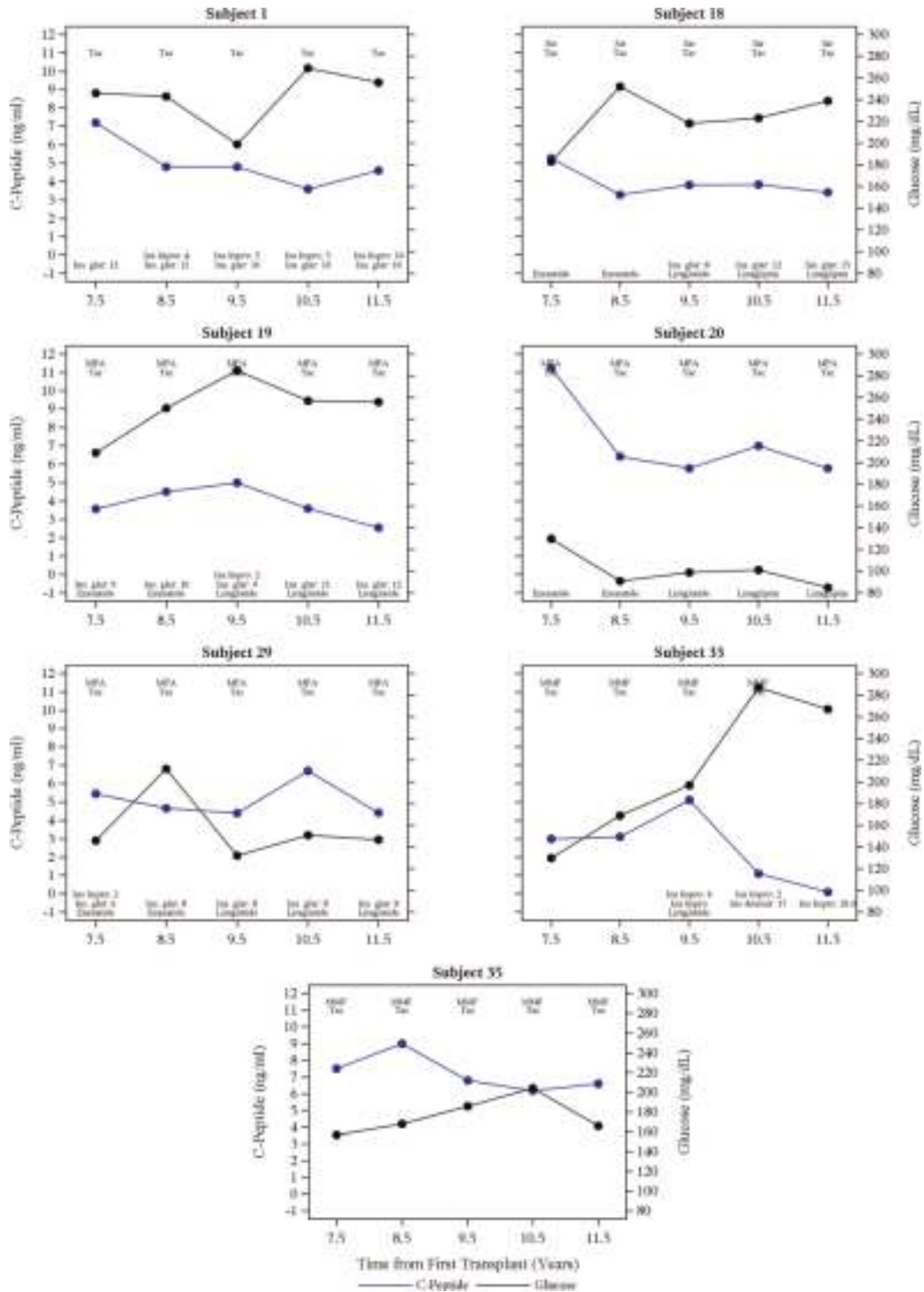


Figure 4: Yearly mixed meal tolerance test 90-min C-peptide (ng/mL) and glucose (mg/dL) levels during the EXIST trial by subject. The immunosuppressive drugs the subject was receiving are annotated at the top of each graph. The diabetic-controlling medications and insulin use and daily units are annotated at the bottom of each graph. EXIST, Extended Immunosuppression in Islet Transplantation.

Another strength of this study is the use of the MMTT to assess islet cell function. The results demonstrate long-term C-peptide persistence in the majority of subjects. All seven subjects maintained islet graft function over a decade from the time of the first islet transplantation, although one patient had allograft failure after 10 years and three had a supplemental islet transplant prior to enrollment in EXIIST. One patient from the original NIS01 trial has remained insulin independent without supplemental islet transplantation or antiglycemic medications for more than 10 years. Even in the absence of long-term insulin independence, subjects experienced relatively stable glucose control over an 11-year period. Over time, a gradual decrease in insulin production, as measured by 90-min C-peptide values with an MMTT, was observed.

Despite the lack of insulin independence in the majority of subjects, the persistent presence of insulin production was associated with near normal HbA_{1c} and no requirement for emergency rescue for hypoglycemia.

After sirolimus was withdrawn, other immunosuppressive medications were well tolerated. One subject remained on the NIS01 IS treatment, which included sirolimus.

It appeared that GLP-1-related therapy was useful in the management of these posttransplant subjects. As such, these drugs may have helped to support continued islet cell function in four of the seven subjects in this trial while still avoiding serious drug–drug interactions with the active immunosuppressive medications used in this protocol.

All subjects received >10 000 IEQ/kg with a median total of 18 721 IEQ/kg. In this small sample, there was no clear correlation between the IEQ/kg transplanted and insulin independence or graft failure, even after multiple transplants. The Edmonton trial used an IL-2-receptor antagonist, a relatively weak agent, as the immunosuppressive induction agent. The more recent use of potent T cell-depleting agents and anti-tumor necrosis factor- α agents allows for better islet transplant outcomes with lower islet-mass infusions (10).

Correlations of basal or 90-min C-peptide levels with glucose levels (both fasting and 90-min MMTT) or with insulin dosage were not statistically significant. These results may be due to the fact that the EXIIST trial was not powered to detect correlations among IEQ/kg infused and maximal C-peptide. Nevertheless, the data suggest that there is need for improvements in the assessment of the determinants affecting islet transplantation success beyond maximal C-peptide and the total islet mass as assessed by IEQ/kg.

One such assessment is the C-peptide-to-glucose ratio. The C-peptide-to-glucose ratio has been used in recent publications to assess islet transplantation success (5), but the strength of our trial is that this ratio has been serially

tested for more than a decade, 2001–2014. Similar to the Saisho and Faradji study (5,11), we conclude that the 90-min ratio was the single strongest factor associated with insulin independence among our subjects.

There was also a gradual decline in islet function over time. Whether this is from islet exhaustion, autoimmune, or alloimmune mechanisms was beyond the scope of this study. In the one subject who experienced late islet allograft failure, there was no obvious alloimmune or autoimmune cause as there were no detectable DSAs, and the GAD 65 antibody was negative. This finding suggests that islets are terminally differentiated and that their function naturally declines.

Although registry studies have reported longer follow-up on some individuals, the seven-subject EXIIST trial is the first prospective multicenter study that evaluated long-term efficacy and safety of islet transplantation for >10 years. Two prior studies had followed patients for 5 years (12,13). The seven subjects who participated in the study are also captured in the National Institute of Diabetes and Digestive and Kidney Diseases Collaborative Islet Transplant Registry (CITR) (14). This registry provides a yearly comprehensive overview of the cumulative safety and efficacy data for islet transplants from 1999 to present. Participation in CITR is intended to provide long-term data to determine whether the usual progression of diabetes complications can be changed by islet transplantation.

A year before the common closeout date, all subjects were contacted regarding options for continued care. All investigators ensured their subjects were able to secure funding for their immunosuppressive medications through their insurance companies independent of the National Institutes of Health or through the opportunity of a research study.

Since the initiation of the Edmonton Protocol and EXIIST follow-up, alternative protocols for human islet transplantation have been instituted. They have shown improved long-term outcomes including near-normal HbA_{1c}, decrease in severe hypoglycemic episodes, a return of hypoglycemia awareness, and long-term islet function is also more common with some centers reporting rates of insulin independence at 3 years of 44% among patients transplanted between 2007 and 2010 (13). Retention of islet graft function (C-peptide ≥ 0.3 ng/mL) for up to 8 years in islet transplant recipients was recently reported by the Collaborative Islet Transplant Registry (15). Similarly, the group from the University of Alberta recently reported sustained islet function as measured by the presence of C-peptide in 73% of their transplanted subjects, with 15% insulin independent at 9 years after transplantation (16).

Thus, the provision of immunosuppressive medications after islet transplantation in the EXIIST study, the long-term follow-up of the Edmonton Protocol, was associated with long-term islet function, excellent glucose control as

determined by the HbA_{1c}, avoidance of severe hypoglycemia, and stable renal function without an increased risk of infection or malignancy over a period of 11 years. Islet function, however, gradually decreased over time, and the reasons for the decline remain to be elucidated. Alternative protocols show improved success and are actively being investigated.

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Disclosure

The authors of this manuscript have no conflicts of interest to disclose as described by the *American Journal of Transplantation*.

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Supporting Information

Additional Supporting Information may be found in the online version of this article.

Figure S1: Yearly 2-hour mixed meal tolerance test results during the EXIIST trial by subject. C-peptide (A) and C-peptide-to-glucose ratio (B) are presented. An asterisk at time -10 indicates the subject was receiving insulin at the time of the test. EXIIST, Extended Immunosuppression in Islet Transplantation; MMTT, mixed meal tolerance test.

Figure S2: Tacrolimus trough level (A) and sirolimus trough level (B) over time by subject. The band represents the switch from the NIS01 study to the EXIIST study. EXIIST, Extended Immunosuppression in Islet Transplantation.