



Ten-Year Outcome of Islet Alone or Islet After Kidney Transplantation in Type 1 Diabetes: A Prospective Parallel-Arm Cohort Study

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OBJECTIVE

The long-term outcome of allogenic islet transplantation is unknown. The aim of this study was to evaluate the 10-year outcome of islet transplantation in patients with type 1 diabetes and hypoglycemia unawareness and/or a functioning kidney graft.

RESEARCH DESIGN AND METHODS

We enrolled in this prospective parallel-arm cohort study 28 subjects with type 1 diabetes who received islet transplantation either alone (ITA) or after a kidney graft (IAK). Islet transplantation consisted of two or three intraportal infusions of allogenic islets administered within (median [interquartile range]) 68 days (43–92). Immunosuppression was induced with interleukin-2 receptor antibodies and maintained with sirolimus and tacrolimus. The primary outcome was insulin independence with A1C ≤6.5% (48 mmol/mol). Secondary outcomes were patient and graft survival, severe hypoglycemic events (SHEs), metabolic control, and renal function.

RESULTS

The primary outcome was met by (Kaplan-Meier estimates [95% CI]) 39% (22–57) and 28% (13–45) of patients 5 and 10 years after islet transplantation, respectively. Graft function persisted in 82% (62–92) and 78% (57–89) of case subjects after 5 and 10 years, respectively, and was associated with improved glucose control, reduced need for exogenous insulin, and a marked decrease of SHEs. ITA and IAK had similar outcomes. Primary graft function, evaluated 1 month after the last islet infusion, was significantly associated with the duration of graft function and insulin independence.

CONCLUSIONS

Islet transplantation with the Edmonton protocol can provide 10-year markedly improved metabolic control without SHEs in three-quarters of patients with type 1 diabetes, kidney transplanted or not.

The demonstration in 2000 that β -cell replacement with allogenic islet transplantation could restore endogenous insulin secretion and near-normal glucose homeostasis was an important landmark for the treatment of type 1 diabetes (1). Since then, islet transplantation has been offered worldwide in >1,000 patients with type 1

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diabetes and hypoglycemia unawareness and/or a kidney graft for end-stage renal disease (2). The favorable early benefit-risk profile of islet transplantation has been reported by numerous single and multicenter studies (3–10), and confirmed in the international Collaborative Islet Transplantation Registry (CITR) (11). Furthermore, islet transplantation appeared superior to optimized medical treatment in several case-control studies (12–15), and a multicenter randomized controlled trial recently demonstrated that islet transplantation was associated with better glucose control at 6 months (16). Other studies also suggest that islet transplantation improves quality of life (16,17) and may favorably impact chronic diabetic complications (18–22). On the other hand, islet graft function may decline with time (4,11), and chronic immunosuppression has been associated with serious adverse events (SAEs) and a decrement in renal function (4,9,11,12). Moreover, the persistence of the early benefit of islet transplantation beyond 5 years can only be speculated from a few series of selected cases (23–28).

Therefore, the aim of the current study was to evaluate the 10-year outcome, in intention to treat, with islet transplantation in patients with type 1 diabetes and hypoglycemia unawareness and/or a functioning kidney graft initially included in two clinical trials. The secondary objectives were to explore the determinants of long-term successful β -cell replacement with islet transplantation.

RESEARCH DESIGN AND METHODS

Study Design

This observational, prospective, parallel-arm, cohort study was designed to evaluate the long-term outcome of allogenic islet transplantation in patients with type 1 diabetes. We enrolled all participants from two single-arm, single-center, phase 2 studies initiated in 2003 at Lille University Hospital to evaluate the 1-year outcome of islet transplantation, performed either alone (ITA) in nonuremic patients (NCT00446264) or after a kidney graft (IAK) in uremic patients (NCT01123187). Study protocols were approved by the institutional review board, and a signed informed consent was obtained from each patient, as previously described (10). The 28 consecutive participants in these two studies received islet transplantation between

13 March 2003 and 1 December 2012. As initially planned for each study, the enrollment was interrupted when the primary outcome (80% insulin independence with adequate glucose control after 1 year) was confirmed in the first 14 participants (sequential triangular design). Participants gave written informed consent to pursue follow-up beyond the 1st year and attended at least yearly routine hospital visits up to 10 years after islet transplantation. The database was frozen on 22 December 2017.

Patients

Enrolled subjects had type 1 diabetes documented for >5 years at the time of islet transplantation and arginine-stimulated C-peptide <0.3 ng/mL. Nonuremic patients had hypoglycemia unawareness and/or documented metabolic lability and an estimated glomerular filtration rate (eGFR) >60 mL/min/1.73 m². Uremic patients had a kidney graft with stable renal function, no episode of kidney graft rejection, and blood pressure in the normal range whatever the use of antihypertensive drugs. In these patients, simultaneous pancreas transplantation had been refused because of age >45 years, severe macroangiopathic complications, or by patient's choice, or performed but followed by a nonimmune complication requiring pancreas graft explantation. In all cases, exclusion criteria included an age <18 or >65 years, a BMI \geq 28 kg/m², albuminuria >300 mg/24 h, unstable arteritis or heart disease, active infection, insulin daily requirements >1.2 units/kg, history of malignancy, smoking, desire for pregnancy, psychiatric disorders, and lack of compliance.

Islet Transplantation

Islet transplantation consisted of up to three sequential islet infusions within 3 months, with the aim of reaching adequate metabolic control without exogenous insulin. Islets were isolated from pancreata harvested in ABO blood type-compatible deceased donors with a negative cross-match (10). The access to the portal vein was gained under general anesthesia by percutaneous catheterization of a peripheral portal branch under ultrasound guidance or by surgical catheterization of a small mesenteric vein. In all cases, heparin (35 units/kg)

was added to the final islet preparation, gently infused by gravity with portal pressure monitoring.

Immunosuppression

The immunosuppression consisted of tacrolimus (Prograf; Astellas, Paris, France), target trough levels at 3–6 ng/mL, and sirolimus (Rapamune; Wyeth Pharmaceuticals, Paris, France), target trough levels at 12–15 ng/mL for 3 months and at 7–10 ng/mL the first year and 5–6 ng/mL thereafter. A five-dose induction course of daclizumab (1 mg/kg) (Zenapax; Roche, Welwyn Garden City, U.K.) was administered biweekly beginning 1 h before the first infusion. For IAK, the median (interquartile range) elapsed time between kidney and islet transplantation was 22 months (18–38). The kidney transplantation had been performed with a standard-of-care protocol, i.e., in most cases antithymocyte antibodies, mycophenolate, and tacrolimus with an initial bolus of 1 g of prednisolone. Steroids had been progressively tapered over 3–9 months until complete discontinuation if there was no sign of kidney rejection. About 12 months after kidney transplantation, mycophenolate was progressively switched to sirolimus to reach blood trough sirolimus levels of 7–10 ng/mL and tacrolimus levels around 5 ng/mL. The blood pressure and renal function had to be normal. When an islet preparation was available, a course of anti-interleukin-2 receptor antibody was performed, repeated for each of the two or three islet injections performed over 3 months.

Follow-up

A comprehensive clinical and biological evaluation was performed before islet transplantation and each year after the first islet infusion, with intermediate routine clinical visits at least twice per year. Daily exogenous insulin requirements, antidiabetic treatments, and adverse events were recorded at each visit. Exogenous insulin was reintroduced when A1C increased above 6.5% (48 mmol/mol) on two consecutive measurements. The following parameters were analyzed using standardized methods unless otherwise indicated: daily glucose profile (mean glucose, SD around mean glucose and percentage of time spent in hypoglycemia <70 mg/dL) assessed with continuous glucose

monitoring (CGM; Medtronic MiniMed, Northridge, CA) for three consecutive days, fasting and postprandial blood glucose and C-peptide (RIA-coat C-peptide; Mallinckrodt, Paris, France) (detection threshold 0.2 ng/mL), plasma creatinine, A1C, and tacrolimus and sirolimus trough levels. The presence and type of autoantibodies GAD, islet cell antibody (ICA), and IA2 were evaluated before transplantation, after each islet infusion, yearly during the follow-up, and, in case of graft loss, 3 months after discontinuation of immunosuppression.

Study Outcomes

The primary outcome was insulin independence, defined as the absence of exogenous insulin therapy associated with $A1C \leq 6.5\%$ (48 mmol/mol). Secondary outcomes were patient survival, yearly incidence of severe hypoglycemic events (SHEs), graft function defined as fasting plasma C-peptide ≥ 0.3 ng/mL, metabolic control assessed by A1C, the CGM daily glucose profile, and the daily exogenous insulin requirement. Primary graft function was evaluated 1 month after the last islet infusion with the β -score, a previously validated composite index ranging from 0 (no graft function) to 8 (excellent graft function) (29,30). This score gives two points for normal fasting glucose (≤ 5.5 mmol/L), $A1C \leq 6.1\%$ (43 mmol/mol), stimulated and/or basal C-peptide (≥ 0.3 nmol/L), and absence of insulin or oral hypoglycemic agent use. No point is awarded if fasting glucose is in the diabetic range (≥ 7 mmol/L), $A1C$ is $\geq 7\%$ (53 mmol/mol), C-peptide secretion is undetectable on stimulation, or daily insulin use is ≥ 0.25 units/kg. One point is given for intermediate values. Graft function was considered optimal when the β -score was 7 or 8, suboptimal when the β -score was 4–6, and poor when the β -score was 3 or less.

We also analyzed renal function with the eGFR calculated with the MDRD formula. Adverse events were classified according to the National Cancer Institute common terminology criteria for adverse events (version 3.0). SAEs (grades 3–5) were monitored and classified as most likely related to the islet transplantation procedure, immunosuppression, or diabetes complications.

Statistical Analysis

All results available at each time point were analyzed in intention to treat (i.e., including patients who had lost graft function and stopped immunosuppression) and expressed as medians (and interquartile range) for continuous variables and as frequencies (and percentages) for categorical variables, without any imputation. Continuous variables were compared between groups with the Mann-Whitney *U* test. Discrete variables were compared with Fisher exact tests. To test the effect of time on the evolution of metabolic and renal measurements, a linear mixed model was applied with the “patient” effect considered as a random effect. Graft function and insulin independence survival rates were estimated with the Kaplan-Meier model. The impact of patient and graft characteristics on these survival rates were estimated with a Cox proportional hazards regression model. A *P* value < 0.05 was considered significant. All statistical analyses were performed with SAS Studio Statistics (version 3.71) and Prism GraphPad (version 8.0.0) software.

RESULTS

Patient Characteristics

A total of 28 patients (14 nonuremic and 14 uremic) were enrolled. The patient characteristics prior to transplantation are presented in Table 1. Three uremic patients had received previous pancreas transplantation (two simultaneously to and one after a kidney graft) and experienced a nonimmunological failure of the pancreas. Each patient initially received two ($n = 10$) or three ($n = 18$) infusions delivered within 68 days (43–91), and, overall, 74 islet infusions were performed. No supplementary islet infusion was performed during the follow-up. At baseline, the clinical and biological characteristics of patients and grafts were not different between uremic and nonuremic patients, except for renal function and BMI (Table 1). Primary graft function, calculated 1 month after the last islet infusion (see RESEARCH DESIGN AND METHODS), was optimal in 18 patients (64%) and suboptimal in 10 patients (36%).

Patient Follow-up

The median follow-up duration was 11.5 years (8.9–12.9), corresponding to a total of 298 patient-years. One IAK patient

with a previous leg amputation died of a stroke 35 months after islet transplantation, with functioning islet and kidney grafts, and 27 patients were alive at the time of this analysis. The overall mortality rate was 0.3% per 100 patient-years. One ITA patient who had lost graft function declined follow-up after the 5-year visit, and one IAK patient moved from the region with a functioning islet graft after the 6-year visit. All other participants had attended each yearly visit, and at the time of this analysis, 27 (96%) and 20 (71%) of the patients initially enrolled completed the 5- and 10-year visits, respectively (Table 2).

Primary Outcome

After islet transplantation, exogenous insulin could be interrupted in all 28 patients, 91 days (61–115) after the first islet infusion. Overall, the Kaplan-Meier estimates of patients remaining off insulin with $A1C \leq 6.5\%$ (48 mmol/mol) were 39% (22–57) at 5 years and 28% (13–45) at 10 years (Fig. 1A). These figures did not differ significantly between ITA and IAK recipients (Fig. 1B). Among the five patients that were insulin independent at 10 years, three patients had received oral antidiabetic medications after 5, 7, and 8 years. In a Cox proportional hazards univariate regression analysis, optimal primary graft function, female sex, longer history of diabetes, and total islet mass infused were associated with retention of insulin independence with $A1C \leq 6.5\%$ after 10 years (Supplementary Table 1).

In patients who experienced optimal primary graft function, the median duration of insulin independence associated with $A1C \leq 6.5\%$ (48 mmol/mol) was 6 years (1.9–10) vs. 0.4 years (0.2–1.1) in those with suboptimal primary graft function (hazard ratio [HR] 0.19 [0.08–0.48], $P = 0.0004$) (Fig. 1C and Supplementary Table 1).

Secondary Outcomes

At last follow-up, graft function persisted in 20 patients (10 ITA and 10 IAK). Six patients lost their graft function while they were still under immunosuppression, 7, 15, 35, and 89 months after ITA and 7 and 10 months after IAK.

The Kaplan-Meier estimates of graft survival were 82% (62–92) and 78% (57–89) after 5 and 10 years, respectively, in the entire study group (Fig. 1D).

Table 1—Baseline patient and graft characteristics of the entire study group and comparison of ITA and IAK recipients before islet transplantation

| | All recipients (n = 28) | ITA recipients (n = 14) | IAK recipients (n = 14) | P value, ITA vs. IAK |
|--|-------------------------------|------------------------------|-----------------------------|-------------------------|
| Sex male | 13 (46) | 7 (50) | 6 (43) | 1 |
| Age (years) | 43 (37–50) | 42 (36–51) | 44 (40–49) | 0.6130 |
| BMI (kg/m ²) | 22.9 (21.3–24.6) | 24.6 (22.9–25.9) | 22.6 (20.2–22.9) | 0.0012 |
| Diabetes duration (years) | 28 (24–31) | 28 (17–31) | 30 (24–34) | 0.3749 |
| Exogenous insulin requirements (IU/kg per day) | 0.57 (0.41–0.74) | 0.6 (0.42–0.73) | 0.54 (0.39–0.74) | 0.5757 |
| No. of severe hypoglycemia events in previous year | 2 (1–5) | 3 (1–7) | 2 (0–3) | 0.4084 |
| No. of autoantibodies | 1 (0–2) | 1 (1–2) | 2 (0–2) | 0.6749 |
| Glycated hemoglobin (%) (mmol/mol) | 8.15 (7.3–8.95) 66 (56–74) | 8.45 (7.3–8.9) 69 (56–74) | 7.9 (7.3–9.2) 63 (56–77) | 0.7789 |
| Mean glucose (CGM) (mg/dL) | 146 (131–208) | 159 (136–210) | 139 (129–186) | 0.3613 |
| SD of mean glucose (CGM) (mg/dL) | 63 (45–77) | 60 (41–87) | 68 (53–77) | 0.4908 |
| Time below range (<70 mg/dL) (CGM) (%) | 9 (3–16) | 14 (3–21) | 9 (3–13) | 0.5053 |
| eGFR (mL/min/1.73 m ²) | 68 (59–84) | 84 (73–89) | 59 (49–64) | <0.0001 |
| No. of islet infusions | 3 (2–3) | 3 (2–3) | 3 (2–3) | 0.6970 |
| Total tissue volume (mL) | 12.3 (8.8–15.2) | 12.5 (10–14) | 11.8 (8.7–16.3) | 0.7743 |
| Total islet mass (10 ³ IEQ/kg) | 13.45 (10.93–15.28) | 12.07 (10.64–14.65) | 13.83 (12.79–15.43) | 0.4025 |
| Islet viability (%) | 93 (90–96) | 94 (91–95) | 93 (89–97) | 0.7988 |
| Islet function (GSIS) | 2.08 (1.57–2.45) | 2.03 (1.48–2.52) | 2.26 (1.62–2.38) | 0.5683 |
| Time from first infusion to insulin independence (days) | 91 (61–115) | 91 (62–115) | 91 (56–111) | 0.8678 |
| Optimal primary graft function | 18 (64) | 9 (64) | 9 (64) | 1 |

Values expressed as medians (IQR) or frequencies (percentages). GSIS, glucose-stimulated insulin secretion; IEQ, islet-equivalent.

The Kaplan-Meier estimates of graft survival were not significantly different after 5 years (79% [47–93] vs. 86% [54–96]) and after 10 years (71% [41–88] vs. 86% [54–96]) in ITA and IAK recipients, respectively (HR 0.55 [0.1–3], $P = 0.4877$) (Fig. 1E and Supplementary Table 1).

In patients who experienced optimal primary graft function, the median duration of graft survival was 10 years (8–10) vs. 4.5 years (0.8–10) in those with suboptimal primary graft function (HR 0.07 [0.01–0.64], $P = 0.0184$) (Fig. 1F and Supplementary Table 1).

In a Cox proportional hazards univariate regression analysis, optimal primary graft function and a longer history of diabetes were associated with higher graft survival at 10 years (Supplementary Table 1).

The median incidence of SHEs per year significantly decreased from 2 (1–5) events per year prior to islet transplantation to 0 (0–0) events at 5 ($P < 0.0001$) and 10 years ($P < 0.0001$), respectively (Table 2).

All metabolic parameters A1C, daily exogenous insulin requirement, mean glucose, SD around mean glucose, and percentage of time spent in hypoglycemia were improved durably over time.

These parameters slightly deteriorated with time but remained significantly improved at 10 years (Table 2).

Immunosuppression

Immunosuppressive drugs were stopped progressively in three out of the six ITA patients who lost graft function, within 3.6 months (2.8–5.8) after C-peptide became undetectable. One patient chose to stop his immunosuppressive treatment after reintroduction of insulin became necessary, despite detectable C-peptide. The last two patients are currently under progressive discontinuation. Immunosuppression was maintained after islet graft loss in two IAK patients with functioning kidney graft. Overall, 6 out of 28 patients (21%; 1 ITA and 5 IAK) had to be switched from sirolimus to mycophenolate after 26.1 months (11.5–43.2), for intolerance.

Adverse Events

All SAEs occurring during and beyond the 1st year are summarized in Supplementary Table 2. Each SAE was classified as most likely related to the infusion procedure, immunosuppression, or complications of type 1 diabetes. During the 1st year posttransplantation, 11 SAEs related to

the infusion procedure were observed, 6 of them involving bleeding, including 3 potentially life-threatening events after percutaneous islet infusion. Five SAEs (hematological disorders, nonopportunistic infections, and diarrhea) were related to immunosuppression. One toe amputation was related to diabetic complications. After 1 year and until 10 years postislet transplantation, eight SAEs related to immunosuppression occurred: four infections (two opportunistic and two nonopportunistic) and four skin carcinomas (two squamous and two basal cell carcinomas). Three of these skin carcinomas, all successfully treated with local excision, occurred in IAK recipients. Eleven diabetes-related macroangiopathic events occurred, nine of them >5 years after the first islet transplantation: five symptomatic events, four of them in the IAK recipients (one stroke in the IAK patient who later died as mentioned above, one myocardial infarct, one pulmonary edema, and two amputations), and six totally asymptomatic events, found by systematic yearly screening, two of them in IAK recipients. The six silent myocardial ischemic episodes were treated by coronary angioplasty stenting in five cases and surgical coronary bypass in the remaining case.

Table 2—Metabolic and renal long-term outcomes in the entire study group

| | 1 year | <i>P</i> value vs. baseline | 5 years | <i>P</i> value vs. baseline | 10 years | <i>P</i> value vs. baseline |
|--|-----------------------------|-----------------------------|-----------------------------|-----------------------------|---------------------------|-----------------------------|
| Patients followed | 28 | | 27 | | 20 | |
| No. of severe hypoglycemia events in previous year | 0 (0–0) | <0.0001 | 0 (0–0) | <0.0001 | 0 (0–0) | <0.0001 |
| Glycated hemoglobin (%) (mmol/mol) | 5.9 (5.5–6.7) 41 (37–50) | <0.0001 | 6.9 (6.1–7.5) 52 (43–58) | <0.0001 | 6.7 (6.1–8) 50 (43–64) | 0.0009 |
| Exogenous insulin requirements (IU/kg per day) | 0 (0–0.04) | <0.0001 | 0 (0–0.36) | <0.0001 | 0.28 (0–0.43) | <0.0001 |
| Mean glucose (CGM) (mg/dL) | 112 (102–133) | <0.0001 | 126 (110–144) | <0.0001 | 118 (113–154) | 0.0007 |
| SD of mean glucose (CGM) (mg/dL) | 22 (15–41) | <0.0001 | 29 (17–52) | <0.0001 | 40 (18–54) | <0.0001 |
| Time below range (<70 mg/dL) (CGM) (%) | 0 (0–5) | <0.0001 | 1 (0–3) | <0.0001 | 3 (0–9) | 0.0012 |
| eGFR (mL/min/1.73 m ²) | 68 (55–81) | 0.8883 | 64 (51–80) | 0.7926 | 54 (43–91) | 0.252 |

Values expressed as medians (IQR) or frequencies (percentages).

Kidney Function

Renal function differed between ITA and IAK at baseline (Table 1). As illustrated in Fig. 2, a slight decrease of eGFR was observed in both groups with time: -1.1 mL/min/1.73 m² per year (-2.5 to 0.1) in ITA and -0.9 mL/min/1.73 m² per year (-2.2 to 0.8) in IAK. This reduction, however, did not reach statistical significance, even after 10 years ($P = 0.52$ in ITA and $P = 0.38$ in IAK, Wilcoxon matched-pairs signed rank test between 10 years and baseline) (Table 2). One IAK patient, who received islet transplantation 45 months after kidney transplantation, while eGFR had decreased to 30 mL/min/1.73 m², remained insulin independent 10 years after islet transplantation. From the three patients referred after pancreas graft failure, one who had received a kidney from a twin living donor lost islet graft function after 10 months. His eGFR was 40 mL/min/1.73 m² at 10 years after the islet transplantation. The second patient remained insulin independent at the last follow-up 8 years after islet transplantation. The third one died with a functioning islet graft as mentioned above.

CONCLUSIONS

In the current study, we evaluated the long-term outcome of allogenic islet transplantation in patients with type 1 diabetes and hypoglycemia unawareness and/or a previous kidney graft. After 10 years, graft function was maintained in 75% of patients, and 28% percent of patients met the study primary outcome: insulin independence with A1C $\leq 6.5\%$ (48 mmol/mol).

In contrast to previous long-term reports of a single case or a small series of selected patients (23–28), we analyzed in this prospective study the 10-year outcome of an entire cohort, with minimal attrition and no secondary rescue islet infusion. Overall, the 10-year results appear comparable to those reported after pancreas transplantation when proposed for the same indications (31,32). Furthermore, half of our patients still maintained A1C level $<7\%$ without SHEs, the alternative end point considered for licensure of islet transplantation in the U.S. (9).

We also confirmed that long-term outcomes were first related to the primary graft function, evaluated 1 month after the last islet infusion (33). However, the precise determinants of early islet graft function remain to be clarified. Indeed, this early proxy reflects not only the mass and quality of transplanted islets but also their initial engraftment. In the present cohort, we deliberately optimized primary graft function by initially administering two or three sequential islet infusions. All patients reached insulin independence, an early outcome that was also associated with longer retention of islet graft function in the CTR (2). In the current study, an optimal primary graft function was associated with prolonged graft function and a median duration of insulin independence with A1C $\leq 6.5\%$ of 6 years. Since partial graft function is sufficient to prevent severe hypoglycemia (30), alternative and less stringent composite end points have been proposed to define success in islet transplantation, based on glucose

control and avoidance of severe hypoglycemia, independently of insulin independence (34). Nevertheless, in the current study, suboptimal graft function was associated with shorter overall islet graft survival. This is in line with the association between initial achievement of insulin independence, another proxy for good primary graft function, and long-term islet graft survival in the CTR (2). Second, we found that the duration of insulin independence was longer in female recipients, independently of their lower body mass. Although the underlying mechanisms remain unclear, recent studies argue for a favorable effect of estrogens on glucose metabolism (35,36).

Importantly, we observed equivalent results when islet transplantation was performed after a kidney graft, in patients with more vascular complications and who had often been refuted for simultaneous pancreas-kidney transplantation. Preexisting immunosuppression and a lower BMI may have contributed to these favorable results. Another key aspect was the stringent selection of the study participants, who had not experienced any acute rejection, uncontrolled hypertension, or macroalbuminuria after kidney transplantation. A progressive switch from mycophenolate to sirolimus was warranted prior to the registration on the islet waiting list, as well as a tapering of steroids. Finally, a previous nonimmunological loss of a pancreas transplant in three patients did not seem to have impaired the results of islet transplantation. Taken together, our results suggest that in uremic patients with

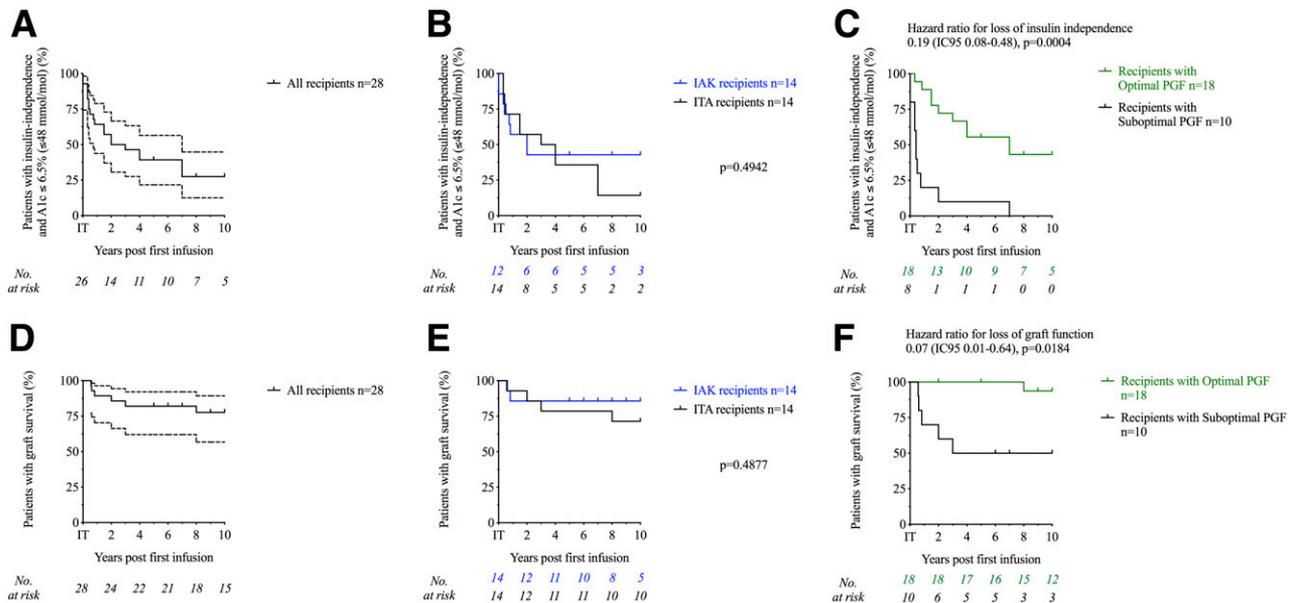


Figure 1—Ten-year Kaplan-Meier estimates of insulin independence with A1C ≤ 6.5% (≤ 48 mmol/mol) and graft survival in the entire cohort in ITA and IAK recipients and in islet recipients with optimal and suboptimal primary graft function (PGF). Insulin independence with A1C ≤ 6.5% (48 mmol/mol) in the entire cohort (95% CIs in dotted black lines) (A), in ITA and IAK recipients (B), and in islet recipients with optimal and suboptimal PGF (C). Graft survival in the entire cohort (95% CIs in dotted black lines) (D), in ITA and IAK recipients (E), and in islet recipients with optimal and suboptimal PGF (F). (A high-quality color representation of this figure is available in the online issue.)

type 1 diabetes, the option of a pancreas or an islet transplantation should be discussed prior to kidney transplantation

to propose the best strategy according to patient characteristics and local possibilities (32,37).

As expected (2), islet infusion was associated with a significant risk of complications (Supplementary Table 2). However, the overall risk profile of intraportal islet infusion observed in the current study appears lower than reported after pancreas transplantation (31,32). All other complications were related to chronic immunosuppression and/or to diabetes. The overall mortality rate observed here (0.3% per 100 patient-years) was equivalent to the mortality rate observed in the Diabetes Control and Complications Trial (DCCT) in patients with type 1 diabetes with little or no complications, and in absence of any immunosuppressive treatment (38). In contrast, the mortality rate reported in patients with characteristics similar to those of the participants enrolled in the current study (i.e., with frequent SHEs or a functioning kidney graft), but non islet transplanted, is three to four times higher and mostly related to SHE or ischemic heart disease (37,39,40). The yearly screening of macroangiopathic diabetes-related complications proposed in this study was more stringent than usually recommended. Likewise, 6 out of 11 events (54%) were detected in absence of any symptoms. Meanwhile, the five symptomatic cardiovascular events occurred >5 years after islet transplantation, and all in IAK

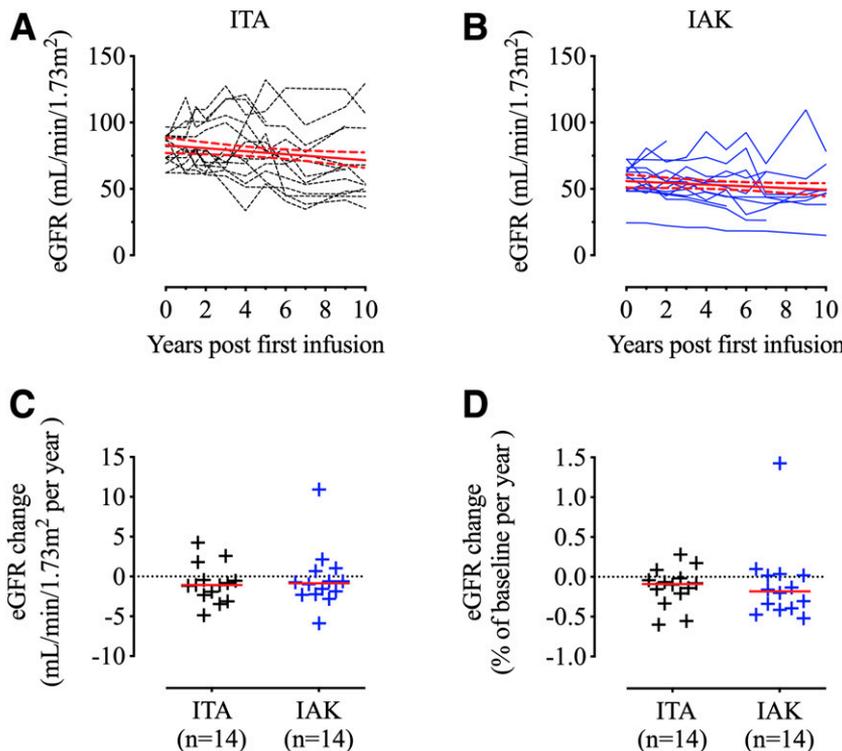


Figure 2—Baseline to 10 years follow-up of kidney function in islet transplantation in ITA and IAK recipients. Individual evolution of eGFR changes over the 10 years of follow-up in ITA (A) and IAK (B) recipients with linear regression (red line) and 95% CI (dotted red lines). Absolute change per year (C) and proportion of change from baseline value (D) in ITA and IAK recipients (red lines summarize the median value). (A high-quality color representation of this figure is available in the online issue.)

patients initially refuted for combined kidney-pancreas transplantation because of preexisting severe diabetes-related complications.

Importantly, the mean decline of eGFR in the entire cohort was similar to the rate expected in the general population >40 years old ($-2 \text{ mL/min/1.73 m}^2$ per year). This was also true for patients with a previous renal graft. Our study, which is in line with some other results (25) but in contrast to earlier ones (41), suggests that improved metabolic control obtained after islet transplantation may exert a favorable effect on kidney function in type 1 diabetes, such as after pancreas transplantation (5,42,43).

One limitation of this study is the lack of a control group of patients receiving optimized insulin therapy or a pancreas transplant. Therefore, whether the improved metabolic control resulting from islet transplantation is balancing the associated risks remains to be demonstrated. Another limitation is the sample size of our study, which was calculated according to its primary metabolic end point. This limits the conclusions that can be drawn about kidney function and macroangiopathic complications. One may also remain cautious when interpreting the difference in early graft function because all participants initially received the same intervention. Moreover, the proposed strategy of initial repeated islet infusion for optimizing primary graft function can be hampered by donor pancreas availability. Finally, we could not explore the impact of the immunosuppression regimen on the islet transplantation long-term outcome. Noteworthy, all participants in our study received low-dose tacrolimus and sirolimus, a drug combination associated with a favorable outcome in the CTR (2). In contrast, immunosuppression was induced here with anti-interleukin-2 receptor antibodies, and not T-cell depletion or TNF- α inhibitors (2,9).

To conclude, the current study provides direct evidence that islet transplantation performed alone or after a kidney graft in patients with type 1 diabetes can markedly improve metabolic control and suppress SHEs during 10 years.

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References

- Shapiro AMJ, Lakey JRT, Ryan EA, et al. Islet transplantation in seven patients with type 1 diabetes mellitus using a glucocorticoid-free immunosuppressive regimen. *N Engl J Med* 2000;343:230–238
- Collaborative Islet Transplant Registry Coordinating Center Collaborative Islet Transplant Registry Tenth Annual Report [Internet], 2015. Available from <http://www.citregistry.org/reports/reports.htm>. Accessed 1 February 2019
- Alejandro R, Lehmann R, Ricordi C, et al. Long-term function (6 years) of islet allografts in type 1 diabetes. *Diabetes* 1997;46:1983–1989

- Ryan EA, Paty BW, Senior PA, et al. Five-year follow-up after clinical islet transplantation. *Diabetes* 2005;54:2060–2069
- Fiorina P, Folli F, Maffi P, et al. Islet transplantation improves vascular diabetic complications in patients with diabetes who underwent kidney transplantation: a comparison between kidney-pancreas and kidney-alone transplantation. *Transplantation* 2003;75:1296–1301
- O'Connell PJ, Holmes-Walker DJ, Goodman D, et al.; Australian Islet Transplant Consortium. Multicenter Australian trial of islet transplantation: improving accessibility and outcomes. *Am J Transplant* 2013;13:1850–1858
- Qi M, Kinzer K, Danielson KK, et al. Five-year follow-up of patients with type 1 diabetes transplanted with allogeneic islets: the UIC experience. *Acta Diabetol* 2014;51:833–843
- Lablanche S, Borot S, Wojtuszczyk A, et al.; GRAGIL Network. Five-year metabolic, functional, and safety results of patients with type 1 diabetes transplanted with allogeneic islets within the Swiss-French GRAGIL Network. *Diabetes Care* 2015;38:1714–1722
- Hering BJ, Clarke WR, Bridges ND, et al.; Clinical Islet Transplantation Consortium. Phase 3 trial of transplantation of human islets in type 1 diabetes complicated by severe hypoglycemia. *Diabetes Care* 2016;39:1230–1240
- Benomar K, Chetboun M, Espiard S, et al. Purity of islet preparations and 5-year metabolic outcome of allogeneic islet transplantation. *Am J Transplant* 2018;18:945–951
- Barton FB, Rickels MR, Alejandro R, et al. Improvement in outcomes of clinical islet transplantation: 1999–2010. *Diabetes Care* 2012;35:1436–1445
- Warnock GL, Thompson DM, Meloche RM, et al. A multi-year analysis of islet transplantation compared with intensive medical therapy on progression of complications in type 1 diabetes. *Transplantation* 2008;86:1762–1766
- Vantyghe MC, Marcelli-Tourvieille S, Fermon C, et al. Intraperitoneal insulin infusion versus islet transplantation: comparative study in patients with type 1 diabetes. *Transplantation* 2009;87:66–71
- Gerber PA, Locher R, Zuellig RA, et al. Glycemia, hypoglycemia, and costs of simultaneous islet-kidney or islet after kidney transplantation versus intensive insulin therapy and waiting list for islet transplantation. *Transplantation* 2015;99:2174–2180
- Holmes-Walker DJ, Gunton JE, Hawthorne W, et al. Islet transplantation provides superior glycemic control with less hypoglycemia compared with continuous subcutaneous insulin infusion or multiple daily insulin injections. *Transplantation* 2017;101:1268–1275
- Lablanche S, Vantyghe M-C, Kessler L, et al.; TRIMECO trial investigators. Islet transplantation versus insulin therapy in patients with type 1 diabetes with severe hypoglycaemia or poorly controlled glycaemia after kidney transplantation (TRIMECO): a multicentre, randomised controlled trial. *Lancet Diabetes Endocrinol* 2018; 6:527–537
- Foster ED, Bridges ND, Feurer ID, Eggerman TL, Hunsicker LG, Alejandro R; Clinical Islet Transplantation Consortium. Improved health-related quality of life in a phase 3 islet transplantation trial in type 1 diabetes complicated by severe hypoglycemia. *Diabetes Care* 2018;41:1001–1008

18. Fiorina P, Folli F, Zerbini G, et al. Islet transplantation is associated with improvement of renal function among uremic patients with type 1 diabetes mellitus and kidney transplants. *J Am Soc Nephrol* 2003;14:2150–2158
19. Thompson DM, Meloche M, Ao Z, et al. Reduced progression of diabetic microvascular complications with islet cell transplantation compared with intensive medical therapy. *Transplantation* 2011;91:373–378
20. Fensom B, Harris C, Thompson SE, Al Mehthel M, Thompson DM. Islet cell transplantation improves nerve conduction velocity in type 1 diabetes compared with intensive medical therapy over six years. *Diabetes Res Clin Pract* 2016;122:101–105
21. Madrigal JM, Monson RS, Hatipoglu B, et al. Coronary artery calcium may stabilize following islet cell transplantation in patients with type 1 diabetes. *Clin Transplant* 2017;31
22. D'Addio F, Maffi P, Vezzulli P, et al. Islet transplantation stabilizes hemostatic abnormalities and cerebral metabolism in individuals with type 1 diabetes. *Diabetes Care* 2014;37:267–276
23. Lakey JRT, Kin T, Warnock GL, et al. Long-term graft function after allogeneic islet transplantation. *Cell Transplant* 2007;16:441–446
24. Berney T, Ferrari-Lacraz S, Bühler L, et al. Long-term insulin-independence after allogeneic islet transplantation for type 1 diabetes: over the 10-year mark. *Am J Transplant* 2009;9:419–423
25. Lehmann R, Graziano J, Brockmann J, et al. Glycemic control in simultaneous islet-kidney versus pancreas-kidney transplantation in type 1 diabetes: a prospective 13-year follow-up. *Diabetes Care* 2015;38:752–759
26. Blau JE, Abegg MR, Flegel WA, Zhao X, Harlan DM, Rother KI. Long-term immunosuppression after solitary islet transplantation is associated with preserved C-peptide secretion for more than a decade. *Am J Transplant* 2015;15:2995–3001
27. Brennan DC, Kopetskie HA, Sayre PH, et al. Long-term follow-up of the Edmonton protocol of islet transplantation in the United States. *Am J Transplant* 2016;16:509–517
28. Williams J, Jacus N, Kavalackal K, et al. Over ten-year insulin independence following single allogeneic islet transplant without T-cell depleting antibody induction. *Islets* 2018;10:168–174
29. Ryan EA, Paty BW, Senior PA, Lakey JR, Bigam D, Shapiro AM. Beta-score: an assessment of beta-cell function after islet transplantation. *Diabetes Care* 2005;28:343–347
30. Vantyghem MC, Raverdy V, Balavoine AS, et al. Continuous glucose monitoring after islet transplantation in type 1 diabetes: an excellent graft function (β -score greater than 7) is required to abrogate hyperglycemia, whereas a minimal function is necessary to suppress severe hypoglycemia (β -score greater than 3). *J Clin Endocrinol Metab* 2012;97:E2078–E2083
31. Gruessner AC, Gruessner RWG. Pancreas transplantation of US and non-US cases from 2005 to 2014 as reported to the United Network for Organ Sharing (UNOS) and the International Pancreas Transplant Registry (IPTR). *Rev Diabet Stud* 2016;13:35–58
32. Wojtuszczyz A, Branchereau J, Esposito L, et al.; TREPID group. Indications for islet or pancreatic transplantation: statement of the TREPID working group on behalf of the Société Francophone du Diabète (SFD), Société Française d'Endocrinologie (SFE), Société Francophone de Transplantation (SFT) and Société Française de Néphrologie–Dialyse–Transplantation (SFNDT). *Diabetes Metab* 2019;45:224–237
33. Vantyghem MC, Kerr-Conte J, Arnalsteen L, et al. Primary graft function, metabolic control, and graft survival after islet transplantation. *Diabetes Care* 2009;32:1473–1478
34. Rickels MR, Stock PG, de Koning EJP, et al. Defining outcomes for β -cell replacement therapy in the treatment of diabetes: a consensus report on the Igls criteria from the IPITA/EPITA opinion leaders workshop. *Transpl Int* 2018;30:1479–1486
35. Liu S, Kilic G, Meyers MS, et al. Oestrogens improve human pancreatic islet transplantation in a mouse model of insulin deficient diabetes. *Diabetologia* 2013;56:370–381
36. Allard C, Morford JJ, Xu B, et al. Loss of nuclear and membrane estrogen receptor- α differentially impairs insulin secretion and action in male and female mice. *Diabetes* 2019;68:490–501
37. Choudhary P, Rickels MR, Senior PA, et al. Evidence-informed clinical practice recommendations for treatment of type 1 diabetes complicated by problematic hypoglycemia. *Diabetes Care* 2015;38:1016–1029
38. Writing Group for the DCCT/EDIC Research Group; Orchard TJ, Nathan DM, Zinman B, et al. Association between 7 years of intensive treatment of type 1 diabetes and long-term mortality. *JAMA* 2015;313:45–53
39. Ortiz F, Harjutsalo V, Helanterä I, Lempinen M, Forsblom C, Groop PH. Long-term mortality after kidney transplantation in a nationwide cohort of patients with type 1 diabetes in Finland. *Diabetes Care* 2019;42:55–61
40. Nathan DM, Cleary PA, Backlund JY, et al.; Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC) Study Research Group. Intensive diabetes treatment and cardiovascular disease in patients with type 1 diabetes. *N Engl J Med* 2005;353:2643–2653
41. Senior PA, Zeman M, Paty BW, Ryan EA, Shapiro AM. Changes in renal function after clinical islet transplantation: four-year observational study. *Am J Transplant* 2007;7:91–98
42. Coppelli A, Giannarelli R, Vistoli F, et al. The beneficial effects of pancreas transplant alone on diabetic nephropathy. *Diabetes Care* 2005;28:1366–1370
43. Kim YC, Shin N, Lee S, et al. Effect of post-transplant glycemic control on long-term clinical outcomes in kidney transplant recipients with diabetic nephropathy: a multicenter cohort study in Korea. *PLoS One* 2018;13:e0195566