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Efficacy and Safety of Allogeneic Islet Transplantation Demonstrated by a Multicenter Clinical Trial in Japan

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Background. Islet transplantation in type 1 diabetes mellitus restores endogenous insulin secretion and hypoglycemia awareness. Although high-quality prospective clinical trials have demonstrated the efficacy of islet transplantation, reports on the clinical outcomes in Asia remain scarce. Therefore, we conducted a clinical trial in Japan to verify the effectiveness of islet transplantation. **Methods.** This multicenter, single-arm study aimed to evaluate the clinical efficacy and safety of immunosuppressive therapy for allogeneic islet transplantation. The immunosuppressive regimens included antithymocyte globulin, calcineurin inhibitors, and mycophenolate mofetil. The primary endpoint was a glycated hemoglobin level of <7.4% on day 365 and the absence of severe hypoglycemic events from 1 mo to 1 y after the first transplantation. **Results.** Eight recipients with evaluation data obtained 1 y after the initial transplantation were included in the efficacy analysis. Of the 8 recipients, 3, 3, and 2 recipients received 1, 2, and 3 islet infusions, respectively. Six recipients (75%) achieved the primary endpoint. The median glycated hemoglobin levels declined from an initial 7.3% to 6.3% and 6.1% on days 375 and 730, respectively, with related improvements in hypoglycemia awareness and glucose variability. No complications associated with intraportal transplantation, such as intraperitoneal hemorrhage or portal vein embolism, were observed. **Conclusions.** Islet transplantation provided near-normal glycemic control and protection against severe hypoglycemic events in patients with type 1 diabetes mellitus in this Japanese cohort. Future studies are needed to confirm whether long-term graft survival can be achieved and whether it is possible to prevent the progression of diabetic complications.

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Type 1 diabetes mellitus (T1D) is a chronic autoimmune disorder characterized by the destruction of insulin-producing beta cells in the pancreas.[1] Despite advancements in insulin therapy, achieving optimal glycemic control remains a challenge and is often accompanied by the risk of hypoglycemia and long-term complications.[2] Islet transplantation for C-peptide-negative T1D has emerged as a potential therapeutic option to restore endogenous insulin secretion and hypoglycemia awareness.[3]

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Derived data supporting the findings of this study are available from the corresponding author, T.A., on request.

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Several clinical trials have investigated the therapeutic effects of islet transplantation. In the Clinical Islet Transplantation (CIT) Consortium Protocol 07 (CIT-07) trial, which was a multicenter prospective clinical trial on islet transplant alone (ITA), T cell–depleting therapy using antithymocyte globulin (ATG) and tumor necrosis factor alpha inhibition induction, combined with maintenance calcineurin inhibitors with mammalian target of rapamycin inhibitors or mycophenolate mofetil (MMF), were adopted as immunosuppressive therapy. Although the insulin independence rate was approximately 50% 1 y posttransplantation, islet transplantation was reported to provide favorable glycemic control, restoration of hypoglycemia awareness, and protection from severe hypoglycemic events (SHEs) in 87.5% of the 48 participants.[4]

In the CIT Consortium Protocol 06, an islet-after-kidney transplant (IAK) with similar immunosuppressive therapy was shown to improve glycemic control and achieve freedom from SHEs while preserving transplant kidney function.[5] Other similar immunosuppressive therapies have shown efficacy in islet transplantation,[6] and T cell–depleting therapy-based immunosuppressive therapies are now mainstream. Recent reports on long-term engraftment demonstrated the potential and durability of this therapeutic approach. In addition, the results of the trial comparing the metabolic efficiency of islet graft to intensive insulin therapy for T1D treatment suggested that islet transplantation is more effective in patients with severe T1D than in those receiving insulin therapy,[7] and the clinical efficacy of islet transplantation is gradually becoming clear.

Although high-quality prospective clinical trials have demonstrated the efficacy of islet transplantation, reports on clinical outcomes in Asia, particularly Japan, remain scarce. Considering the noted variations in islet function between Japanese and Western patients in genetic analysis studies,[8] validating islet transplantation outcomes in such patients is imperative.

In Japan, owing to donor shortages, islet transplantation is performed not only using donors after brain death (DBDs) but also using donors after circulatory death (DCDs) and elderly donors. Islet transplantation results from DCDs have been reported in Japan; islet transplantation using a method similar to the Edmonton protocol has been reported to have relatively favorable short-term results after transplantation,[9] but the long-term graft engraftment rate is inadequate.[10] This report is limited by the fact that islet transplantation with immunosuppressive therapy did not rely on T cell–depleting therapy and was based on a retrospective analysis; therefore, it does not provide sufficient evidence. Whether islet transplantation outcomes in Asian populations, especially in the Japanese population, align with international data remains unclear.

Our multicenter collaborative clinical trial is currently underway to assess the clinical efficacy of islet transplantation in Japan. This trial aimed to provide high-quality prospective data on the outcomes of islet transplantation using both DBDs and DCDs, thereby shedding light on the effectiveness of this therapeutic approach in the Japanese population.

MATERIALS AND METHODS

Study Design

This prospective, open-label, multicenter, single-arm trial was conducted at 7 centers in Japan and aimed to evaluate the clinical efficacy and safety of immunosuppressive therapy for allogeneic islet transplantation in patients with T1D using DBDs and DCDs. The primary endpoint was the achievement of a glycated hemoglobin (HbA1c) level of <7.4% at day 365 and the absence of SHEs from 1 mo to 1 y after the first islet transplantation. Initially, Japan used the standard HbA1c measurement established by the Japan Diabetes Society (JDS), which set the HbA1c target for this study at 7.0%. Subsequently, the internationally recognized National Glycohemoglobin Standardization Program (NGSP) was adopted in Japan. An HbA1c (JDS) level of 7.0% is equivalent to an HbA1c (NGSP) level of 7.4%; therefore, an HbA1c (NGSP) level of <7.4% was established as the study endpoint. In this study, HbA1c values are reported as NGSP in the Results section.

Key secondary endpoints included the achievement of an HbA1c level of <7.4% and absence of SHEs at 730 d after the first transplant; the proportion of patients with an absence of SHEs between 90 and 730 d after the first transplant; and the proportion of patients who achieved insulin independence, which was confirmed by meeting the following criteria during a 7-d period without using insulin: HbA1c <7.4%, fasting serum glucose <126 mg/dL, fasting capillary glucose levels >140 mg/dL ≤3 times, and at least 1 serum fasting or stimulated C-peptide level ≥0.5 ng/mL between 90 and 730 d after the first transplant. Other efficacy endpoints included changes in HbA1c level and exogenous insulin use, Clarke score,[11] glycemic lability index,[12] hypoglycemia score (HYPO),[12] and β score.[13] Safety endpoints included the incidence of severe adverse events (SAEs) related to islet transplantation or immunosuppression. AEs were evaluated using the Common Terminology Criteria for Adverse Events version 4.0.

The first patient gave consent in October 2013. The study period was 10 y and 3 mo, with an enrollment period of 8 y and a treatment period of 2 y and 3 mo from the time of initial islet transplantation. All patients provided informed consent, and the protocol was approved by the Specially Certified Committee for Regenerative Medicine, based on the Act on Securing Safety of Regenerative Medicine (Act No. 85 of 2013). This trial was registered in the University Hospital Medical Information Network Clinical Trials Registry (No. UMIN000003977).

Study Eligibility

Recipient inclusion criteria were as follows: age 18–65 y and T1D for >5 y; absence of stimulated C-peptide; a history of SHEs in the prior 12 mo, despite strict medical care provided by a diabetologist; self-monitoring of blood glucose levels (≥4 times daily); and the use of an insulin pump or administration of ≥3 injections of insulin daily. Each diabetes specialist confirmed that the patient was unable to achieve glycemic control without hypoglycemic episodes.

In cases of IAK, patients also had to be at least 6 mo post–kidney transplantation, have a creatinine of ≤1.8 mg/dL, and no sustained increase in serum creatinine level (≤0.2 in the past 6 mo). Exclusion criteria were as follows: body weight >80 kg or body mass index (BMI) >25 kg/m^2, insulin requirement >0.8 units/kg/d, HbA1c level >10%, estimated glomerular filtration rate <60 mL/min/1.73 m^2, history of panel-reactive anti-HLA antibodies by flow cytometry, and significant comorbid conditions. Each recipient was allowed up to 3 islet transplantations until insulin independence was achieved. Recipients were selected on the basis of blood type, history of previous islet transplantation with the potential for insulin independence, and long waiting period.

Donor Selection

Pancreases were obtained from both DBDs and DCDs who were between 18 and 70 y of age when these were not donated for solid pancreas transplantation for reasons such as high BMI or donor age. In DCDs, after obtaining the donor family's consent at the time of brain death confirmation, a double-balloon catheter was inserted into the aorta to prevent warm ischemic damage to the pancreas, and in-situ regional organ cooling was initiated. Standard criteria for donor exclusion were applied to minimize the risk of transmission of donor-derived infections. The donor exclusion criteria included an HbA1c level >6% and a history of pancreatitis.

Islet Isolation and Transplantation

Harvested pancreases were transported in the chilled University of Wisconsin solution or with a 2-layer method[14] using perfluorocarbon and ETK solutions (Otsuka Pharmaceuticals, Tokyo, Japan). Pancreatic islets were isolated locally from facilities that maintained the appropriate practice guidelines within each institution. The method for pancreatic islet isolation has been previously reported.[15] Pancreatic specimens were digested using Liberase MTF C/T GMP grade (Roche Molecular Biochemicals, Indianapolis, IN). Islets were isolated using the automated method described by Ricordi et al[16] and purified using continuous iodixanol density gradients. The release criteria, such as containing >5000 islet equivalents (IEQ)/kg, were identical to those of the Edmonton protocol.[17] The islets were cultured free-floating in the culture medium for approximately 12 h. Islet preparation was performed via percutaneous transhepatic delivery into the portal vein under radiological guidance. The recipients received intravenous insulin and heparin during the peritransplantation period.

Immunosuppression

Induction immunosuppression, initiated on day −1, consisted of ATG (0.5 mg/kg of recipient body weight); 1.83 mg/kg was administered every 24 h for 3 courses (one course was administered over 12 h). The total ATG dose was 6.0 mg/kg with etanercept (25 mg subcutaneously 1 h pretransplantation, followed by days 3, 7, and 10). Basiliximab (20 mg intravenously on days 0 and 4) was replaced with ATG during the subsequent transplantation.

Maintenance immunosuppression was initiated with tacrolimus and MMF (500–1500 mg/d). Tacrolimus was dose-controlled for the first 3 patients (group 1), with target trough concentrations of 3–6 ng/mL. The protocol was then modified on the basis of the settings of other trials[4] and adjusted to target trough levels of 10–12 ng/mL for the first 3 mo posttransplant, 8–10 ng/mL from 3 to 6 mo posttransplant, and 6–8 ng/mL thereafter. Five patients were adjusted according to the modified protocol (group 2). If the patient was taking cyclosporine after kidney transplantation, cyclosporine was allowed instead of tacrolimus at a trough concentration of 150–200 ng/mL.

Health-related Quality of Life, Functional Health Status, and Health Utility Survey

The Short Form 36 Health Survey (SF-36),[18] version 2 measures several dimensions of functional health status and health utility. The SF-36 consists of 8 scaled scores, and each scale is transformed into a 0–100 scale on the assumption that each question carries equal weight. All patients who requested and were waiting for transplantation were surveyed. After the first transplantation, they were surveyed at 180, 365, and 730 d after transplantation.

Statistical Analysis

Of the 17 islet transplants performed in Japan to date, 12 were considered successful with respect to the primary endpoint of this clinical trial. This was set as the target (expected rate) to be achieved for the primary endpoint of the study. In contrast, the threshold rate was set at 40%, based on the first-year islet graft survival rate before the introduction of the Edmonton protocol.[19] Assuming a 1-sided significance level of 5% and power of 80%, we calculated that approximately 20 patients would be needed, which was the initial target number of patients. However, based on the results of other studies,[4,5] further effectiveness was expected, and it was determined that the achievement target could be changed to 90%. When the expected rate was changed to 90%, and the threshold rate remained at 40%, the number of cases required by the exact method based on the binomial distribution was 6, assuming a 1-sided significance level of 5% and a power of 80%. The target number of patients was 20, as originally planned, but the plan included interim monitoring after each primary endpoint result was known, and the posterior probability of the percentage of achievement was estimated in a Bayesian fashion. If the probability of the proportion of patients achieving a primary endpoint of >40% surpassed 90%, early discontinuation of the study (effective termination) was considered.

Data were presented as the median interquartile range (IQR) unless otherwise stated. Mann-Whitney *U* tests were used for comparisons of 2 independent groups, and the Wilcoxon signed-rank test was used for comparisons of paired data. The survival of graft function was graphically represented using Kaplan-Meier actuarial curves, and the log-rank test was performed to compare the groups. A P value of <0.05 was used to determine statistical significance. Data were processed and analyzed using JMP Pro 17 (SAS Institute Inc, Cary, NC).

RESULTS

Recipient and Donor Characteristics

The pretransplant characteristics of the recipients are shown in Table 1. The 8 recipients had a median (IQR) age of 48.0 (43.2–56.0) y at the time of the first islet transplant and included 5 women (62.5%). Five recipients were categorized as ITA and 3 as IAK. The median BMI was 20.2 (18.1–22.6) kg/m^2. The median HbA1c level was 7.3% (7.0%–8.0%), and the median insulin requirement was 0.69 (0.57–0.86) units/kg/d. The baseline autoantibody titers are shown in Table 1. All recipients had experienced >1 SHE before enrollment in the study.

The donor/pancreas graft characteristics are shown in Table 2. Twenty islet isolates were obtained from 5 DCDs and 15 DBDs; 15 isolates met the transplant criteria and were transplanted. Islet isolation and transplantation were performed at only 4 of 7 centers participating in the study. Facility A conducted 14 of 20 isolations and 12 of 15 transplants. Facility A mainly used 2-layer method as a cold storage method. Three patients received a single islet transplant, 3 received 2 transplants, and 2 received 3 transplants. The median (IQR) age of donors in cases that resulted in transplantation was 43 (39–46) y, including 3 with DCDs and 12 with DBDs. The median (IQR) of the cold ischemic time was 406 (335–442) min. The median

TABLE 1.

Pretransplant characteristics of the recipients

	Recipient no.									
	Group 1			Group 2						
Recipient characteristics	1	2	3	4	5	6	7	8	Median (IQR)	Percentage
Age at first transplant, y	53	42	43	46	44	60	57	50	48 (43–56)	–
Sex (female or male)	Male	Female	Female	Female	Male	Male	Female	Female	–	62.5%, Female
Weight, kg	65.6	47.8	37.3	52.6	58.3	70.7	40	45	50.2 (41.3–63.8)	–
BMI, kg/m^2	20.8	19.8	17.6	19.4	23.4	23.2	17.2	20.5	20.2 (18.1–22.6)	–
HbA1c, %	7.1	8.1	7.2	7.4	6.7	10.2	7.0	7.7	7.3 (7.0–8.0)	–
Insulin requirement										
Units/day	47	43	35	30	38	52	20	26	36.5 (27–46)	–
Units/kg/day	0.72	0.90	0.94	0.57	0.65	0.74	0.50	0.58	0.69 (0.57–0.86)	–
Autoantibodies										
Anti-insulin, nUnits/mL	476	303	124	125	400	335	314	125	309 (125–384)	–
Anti-GAD65, Units/mL	0.7	5.3	0.3	1.4	2.3	230.8	5.1	5	3.7 (0.9–5.3)	–
Anti-ICA512, Units/mL	0.4	1.7	0.4	0.4	0.6	0.4	0.4	0.4	0.4 (0.4–0.6)	–
Clarke score	6	3	5	4	2	6	6	5	5 (3–6)	–
HYPO score	4848	4254	818	966	402	892	5622	900	933 (837–4700)	–
SHE 1 y pretransplant, N	12	3	2	30	1	12	1	12	8 (1–12)	–
Glycemic LI	543	1054	528	352	289	218	431	440	436 (305–539)	–
Creatinine, mg/dL	0.79	0.5	0.5	0.9	1.1	0.9	0.57	0.78	0.79 (0.52–0.90)	–
Transplant type	ITA	ITA	ITA	IAK	IAK	ITA	ITA	IAK	–	62.5%, ITA

BMI, body mass index; HbA1c, glycated hemoglobin; HYPO, hypoglycemia; IAK, Islet-after-kidney transplantation; IQR, interquartile range; ITA, Islet transplant alone; LI, lability index; SHE, severe hypoglycemic event.

total dose was 832 313 IEQ/patient (range, 446 000–1 260 731 IEQ), with a median of 16 012 IEQ/kg of recipient body weight (range, 8052–31 518 IEQ/kg).

Clinical and Metabolic Outcomes

The primary endpoint of achieving an HbA1c <7.4% on day 365 and the absence of severe SHEs on day 365 was achieved in 75% of the patients (6/8; 95% confidence interval, 35%-97%; 90% confidence interval, 40%-95%). Four patients (57.1%) met the primary endpoint criteria as evaluated on day 730 (Figure 1A). An interim monitoring was conducted in accordance with the protocol. The beta distribution of 12.5 was adopted as the prior distribution, and the posterior probability of the percentage of achievement was estimated

TABLE 2.

Donor/pancreas graft characteristics

	Group 1									Group 2
Recipient no.	1			2	3	4		5		6
Tx	1st	2nd	3rd	1st	1st	1st	2nd	1st	1st	2nd
Facility	A	A	A	B	C	A	A	D	A	A
Donor age, y	66	37	39	41	45	46	63	45	20	43
Donor sex	Female	Male	Female	Female	Female	Male	Female	Male	Male	Female
Cause of death	CVA	CVA	CVA	Anoxia	Anoxia	CVA	CVA	Anoxia	Trauma	CVA
DBD or DCD	DBD	DBD	DBD	DCD	DBD	DBD	DBD	DCD	DCD	DBD
Cold storage method	TLM	TLM	UW	UW	UW	TLM	TLM	UW	TLM	TLM
Liberase MTF C/T Lot number	14029500	10485900	10485900	14131900	14131900	10485900	11897500	11307400	11897500	19661400
Pancreas warm ischemia time, min	0	0	0	15	0	0	0	10	3	0
Pancreas cold ischemia time, min	406	411	293	310	72	415	551	337	539	335
Total IEQ transplanted (per Tx)	362 700	426 000	357 522	446 000	565 008	356 179	548 992	469 408	497 375	434 239
Total IEQ/kg/recipient (per Tx)	5529	6494	5450	9331	15 148	6771	10 437	8052	7035	6142
Islet purity, %	30	40	30	50	60	60	90	30	50	50

CVA, cerebrovascular accident; DBD, donor after brain death; DCD, donor after circulatory death; IEQ, islet equivalent; MTF, mammalian tissue free; TLM, 2-layer method; Tx, transplant; UW, University of Wisconsin solution.

using Bayesian methodology. The probability of achievement exceeding 40% was 99.9%, surpassing the predefined target of 90%. Consequently, the criteria for early termination due to effectiveness were satisfied, leading to the premature termination of the study.

None of the patients were free of SHEs in the year before enrollment, and SHEs were eliminated posttransplant in all patients by day 365 and in 4 patients (57.1%) by day 730 (Figure 1B). The median HbA1c level decreased from 7.3% at baseline to 6.2% on day 75 ($P = 0.02$), 6.6% on day 180 ($P = 0.02$), 6.3% on day 365, and 6.1% on day 730 ($P = 0.02$; Figure 1C). The median insulin use dropped from 0.69 units/kg/d at baseline to 0.35 units/kg/d at day 75 ($P = 0.008$), 0.34 units/kg/d at day 180 ($P = 0.008$), 0.37 units/kg/d at day 365, and 0.34 units/kg/d at day 730 ($P = 0.02$; Figure 1D). Insulin independence was achieved in 0% of the patients on day 365 and in 28.6% (2 patients) on day 730 (Figure 1E).

All patients exhibited impaired awareness of hypoglycemia at baseline (Clarke score 5.0 [3.2–6.0]), which was abolished after transplant (Clarke score 1.5 [1.0–3.5] at day 365, $P = 0.02$ and 1.0 [0–1.5] at day 730, $P = 0.03$; Figure 2A). Hypoglycemia severity, reflected by the HYPO at baseline (933.0 [836.5–4699.5]), improved after transplantation (143.0 [32.5–2411.5] at day 365 and 104.0 [26.0–258.5] at day 730, $P = 0.03$; Figure 2B). Glycemic lability was also elevated at baseline (lability index 435.5 [304.8–539.3] mmol/L^2/h/wk^{-1}) and was reduced significantly after transplant (125 [69.8–352.5] mmol/L^2/h/wk^{-1} at day 365, $P = 0.008$ and 89 [119–243] mmol/L^2/h/wk^{-1} at day 730, $P = 0.02$; Figure 2C). The β-score, which is calculated on the basis of HbA1c, insulin requirement, fasting blood glucose, and basal and stimulated C-peptide and is one of the indicators to assess islet function, clearly improved after transplantation (1 [0–1] at baseline; 4.5 [2–6] at day 365, $P = 0.02$ and 5 [2.8–7] at day 730, $P = 0.03$; Figure 2D).

The proportions of patients with a functioning islet graft, defined as a basal or stimulated serum C-peptide level >0.3 ng/mL, were 87.5% and 75% at days 365 and 730, respectively (Figure 3A). A comparison of the graft survival rates between groups 1 and 2 showed that while 100% of the patients in group 2 had functioning grafts until day 730, in group 1, the graft survival rate was 66% on day 365 and 33% on day 730, with group 2 having a significantly higher graft survival rate than group 1 (Figure 3B; $P = 0.004$).

After transplantation, almost all 8 scales of the SF-36 showed improvements (increases) over time (Table 3). These results suggest that the quality of life could be improved in the group that received the transplant compared with the values in the population indicated for islet transplantation.

Adverse Events

The adverse events that occurred in each recipient are listed in Table 4. When multiple identical adverse events occurred in the same case, the worst grade was listed. Three SAEs were reported, all of which were neutropenia associated with immunosuppressive therapy. No procedure-related bleeding events occurred in 15 percutaneous cannulations of the portal vein in the 8 patients. The median creatinine level was 0.79 mg/dL before transplantation and 0.73 mg/dL at day 365 after the initial transplantation (Figure 1F), indicating that renal function was maintained. None of the SAEs resulted in death or disability.

DISCUSSION

This multicenter prospective clinical trial aimed to evaluate the clinical efficacy and safety of allogeneic islet transplantation in patients in Japan with T1D using DBDs and DCDs. To our knowledge, this is the first prospective clinical trial evaluating the efficacy and safety of islet

7			8		Median		Failed islet isolation					Median	
1st	2nd	3rd	1st	2nd	(IQR)	Percentage						(IQR)	Percentage
A	A	A	A	A	–	80%, A	A	A	D	D	D	–	40%, A
43	39	46	60	42	43 (39–46)	–	30	60	39	19	68	39 (25–64)	–
Male	Male	Male	Female	Female	–	53.3%, Female	Female	Male	Female	Male	Male	–	40%, Female
CVA	Anoxia	Anoxia	CVA	CVA	–	60%, CVA	CVA	CVA	Anoxia	Trauma	CVA	–	60%, CVA
DBD	DBD	DBD	DBD	DBD	–	20%, DCD	DBD	DBD	DCD	DCD	DBD	–	40%, DCD
TLM	TLM	TLM	TLM	TLM	–	73.3%, TLM	TLM	TLM	UW	UW	UW	–	40%, TLM
19661400	19661400	34056100	34056100	34056100	–	–	14029500	14457200	13171900	13171900	19661700	–	–
0	0	0	0	0	0 (0–0)	–	0	0	11	19	0	0 (0–15)	–
452	426	354	405	458	406 (335–452)	–	263	350	647	383	629	383 (307–638)	–
485150	326446	449135	289579	469877	446000 (357522–485150)	–	238266	263834	182910	275420	180715	238266 (181813–269627)	–
12129	8161	11228	6435	10442	8052 (6435–10442)	–	NA	NA	NA	NA	NA	NA	–
50	90	40	60	60	50 (40–60)	–	40	35	10	30	10	30 (10–38)	–

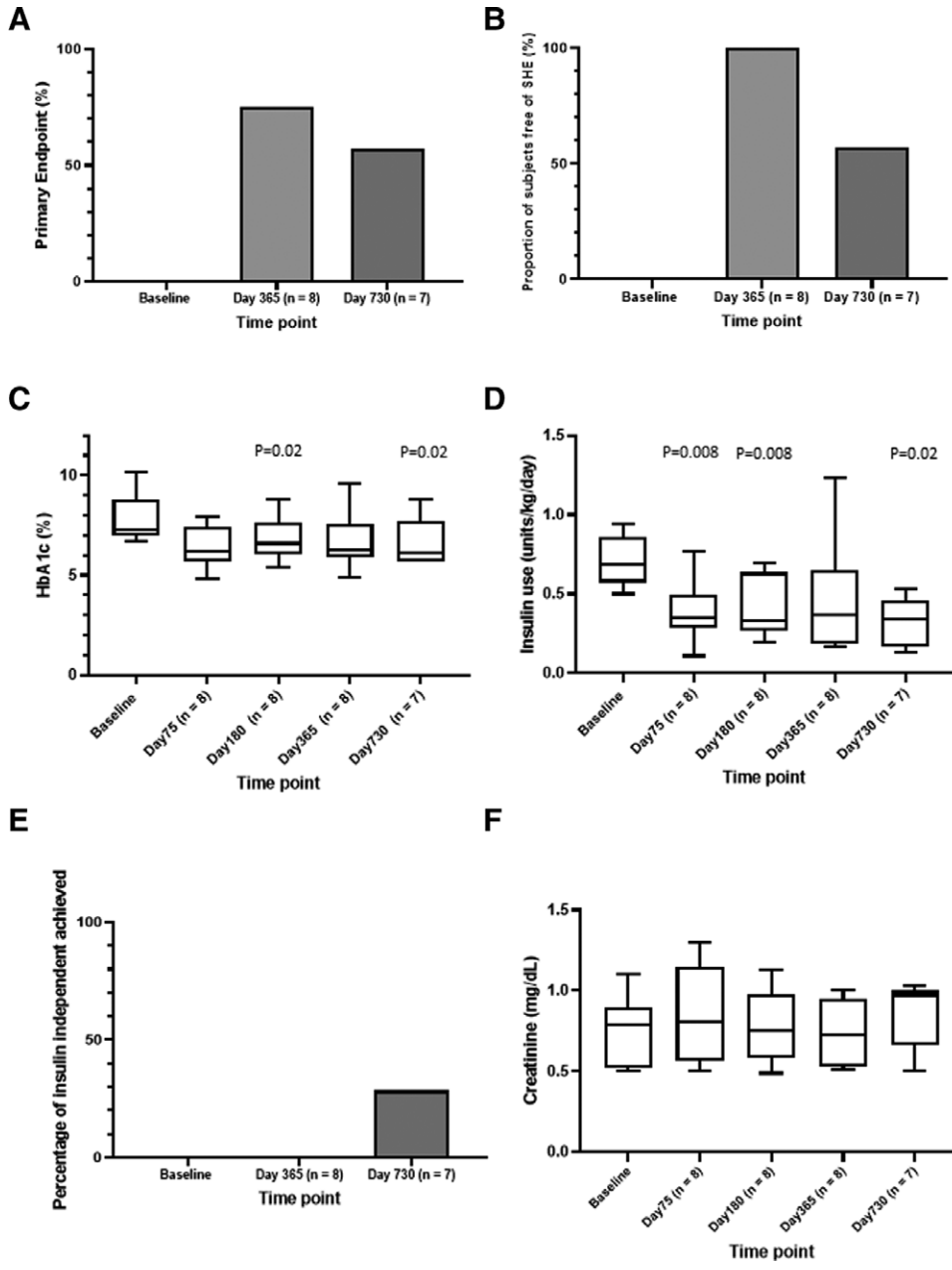

FIGURE 1. Primary endpoint and key secondary endpoints. A, The primary endpoint of achieving HbA1c <7.4% on day 365 and the absence of SHEs on day 365 is achieved in 75% of the patients. A total of 57.1% of the participants met the primary endpoint criteria evaluated on day 730. B, SHEs are eliminated posttransplant in all patients by day 365 and 57.1% by day 730. C, The median HbA1c levels decreased from 7.3% at baseline to 6.2% on day 75 ($P = 0.02$), 6.6% on day 180 ($P = 0.02$), 6.3% on day 365, and 6.1% on day 730 ($P = 0.02$). D, The median insulin use drops from 0.69 units/kg/d at baseline to 0.35 units/kg/d at day 75 ($P = 0.008$), 0.34 units/kg/d at day 180 ($P = 0.008$), 0.37 units/kg/d at day 365, and 0.34 units/kg/d at day 730 ($P = 0.02$). E, Insulin independence is achieved in 0% of the patients on day 365 and in 28.6% on day 730. F, The median creatinine level was 0.79 mg/dL before transplantation and maintained at day 365 and day 730 after the initial transplantation. HbA1c, glycated hemoglobin; SHE, severe hypoglycemic event.

transplantation in Japan and Asia. As a result, islet transplantation is now fully covered by the healthcare system in Japan.

Patients who underwent islet transplantation showed improved glycemic control to near-normal levels after transplantation with reduced insulin use and were free from SHEs. Various indices showed improvement in blood glucose instability and severity of hypoglycemic symptoms. In addition, improvements in the health-related quality of life were confirmed, as in other studies.[20]

We used a protocol of induction immunotherapy with ATG and maintenance immunotherapy with tacrolimus and MMF with etanercept administered early after transplantation, which has been shown to be effective for islet transplantation in Japanese patients. This trial is significant because it addressed the scarcity of data on islet transplantation outcomes in Asian populations, particularly in Japan. By assessing key endpoints, such as glycemic control, hypoglycemia incidence, and islet graft survival, our study aimed to provide valuable insights into the effectiveness of this therapeutic

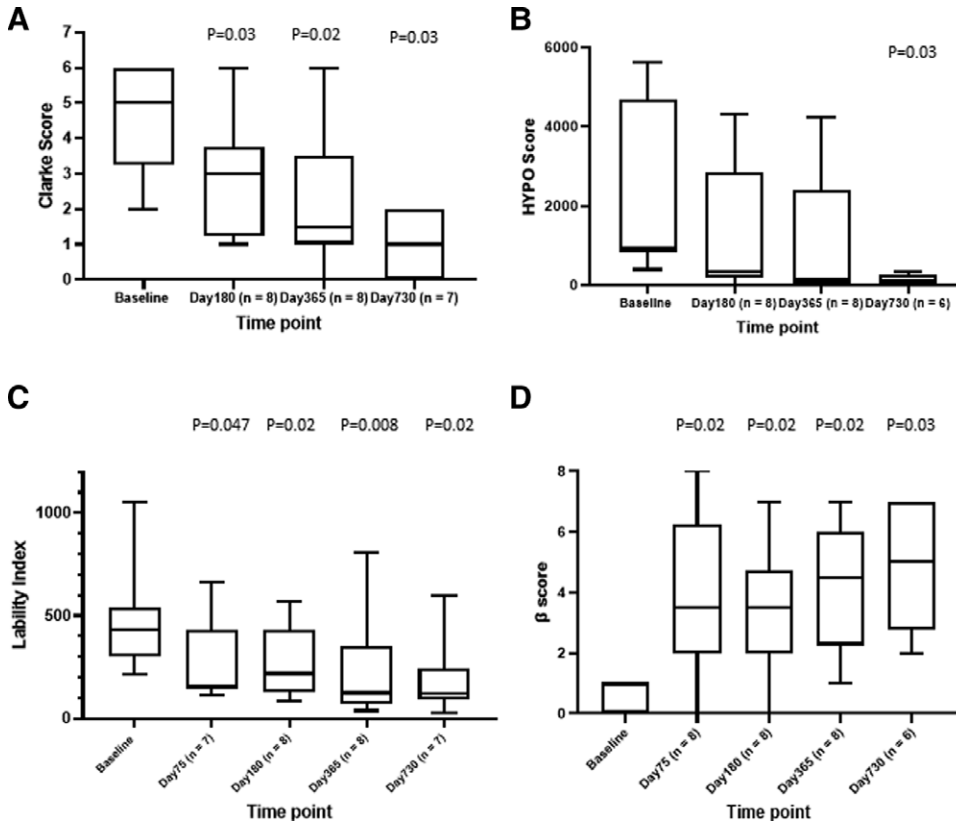

FIGURE 2. Other efficacy endpoints. A, Clarke score is 5.0 (3.2–6.0) at baseline, which is abolished after transplant (Clarke score 1.5 [1.0–3.5] at day 365, $P = 0.02$ and 1.0 [0–1.5] at day 730, $P = 0.03$. B, Hypoglycemia score at baseline (933.0 [836.5–4699.5]) improves after transplantation (143.0 [32.5–2411.5] at day 365 and 104.0 [26.0–258.5] at day 730, $P = 0.03$. C, Glycemic lability is also elevated at baseline (lability index 435.5 [304.8–539.3] mmol/L^2/h/wk^{-1}) and reduces significantly after transplant (125 [69.8–352.5] mmol/L^2/h/wk^{-1} at day 365, $P = 0.008$ and 89 [119–243] mmol/L^2/h/wk^{-1} at day 730, $P = 0.02$). D, The β-score improves after transplantation (1 [0–1] at baseline, 4.5 [2–6] at day 365, $P = 0.02$, and 5 [2.8–7] at day 730, $P = 0.03$). HYPO, hypoglycemia score.

approach in the Japanese population. To date, >4000 islet transplants have been performed worldwide, most of which have been performed in Europe and North America.[21] Only a few cases have been performed in Japan and other Asian countries, and reporting the results of this clinical trial is important because there have been reports of racial differences in the pathogenesis of diabetes mellitus.[8]

Our results indicated that the immunosuppressive regimen, particularly the modified protocol used in group 2, significantly influenced graft survival rates. Group 2, which received maintenance immunosuppression with tacrolimus targeting higher trough levels, demonstrated a significantly higher graft survival rate than group 1. This underscores the importance of immunosuppressive regimen optimization to enhance long-term graft outcomes after islet transplantation. In islet transplantation in North America and Europe, including the Edmonton protocol,[17] rapamycin, although used less frequently these days,[22] was previously often used in addition to tacrolimus for maintenance immunosuppressive therapy, and tacrolimus concentrations are relatively low. When combined with MMF, as in our trial or an Australian trial,[6] we may have to be cautious about lowering the blood concentration of tacrolimus.

In the CIT-07 trial, which was conducted using an immunosuppressive protocol similar to ours, the median transplanted islet dose was 11 972 IEQ/kg body weight. In this trial, the median HbA1c level was 5.6%, and the insulin independence rate was 52% at 1 y posttransplant.[4] Similarly, in an Australian trial that used induction immunosuppressive therapy with ATG, the median transplanted islet dose was 15 366 IEQ/kg body weight. The median HbA1c level 1 y posttransplant was 6.5%, and the insulin independence rate 2 y posttransplant was 45%.[6] In contrast, in our study, although 16 012 IEQ/kg islets were transplanted, the HbA1c level was 6.3% at 1 y and the insulin independence rate was only 28.6% at 2 y. Compared with previously reported trial results, our results seem comparable with those of previous reports in terms of stabilization of blood glucose levels and improvement in the severity of hypoglycemia. Nevertheless, the insulin independence rate in our study is substantially lower, and the outcomes are less favorable compared with other cohorts. Insulin independence was not a primary objective and was not actively pursued during the study. This decision was also influenced by the patient's reluctance to discontinue insulin therapy. Despite this background, the low insulin independence rate may be due to the involvement of several factors discussed below.

The efficacy and safety outcomes observed in our study are consistent with those of previous trials conducted in Western populations, indicating the robustness of islet transplantation as a therapeutic option for T1D across diverse patient demographics. However, differences in immunosuppressive protocols and patient characteristics underscore the need for region-specific considerations when optimizing transplant outcomes. From the large cohort of the Collaborative Islet Transplant Registry, 4 factors have been reported to be associated with the favorable outcome of islet transplantation: recipient age 35 y or older, total infused islets ≥325 000 IEQs,

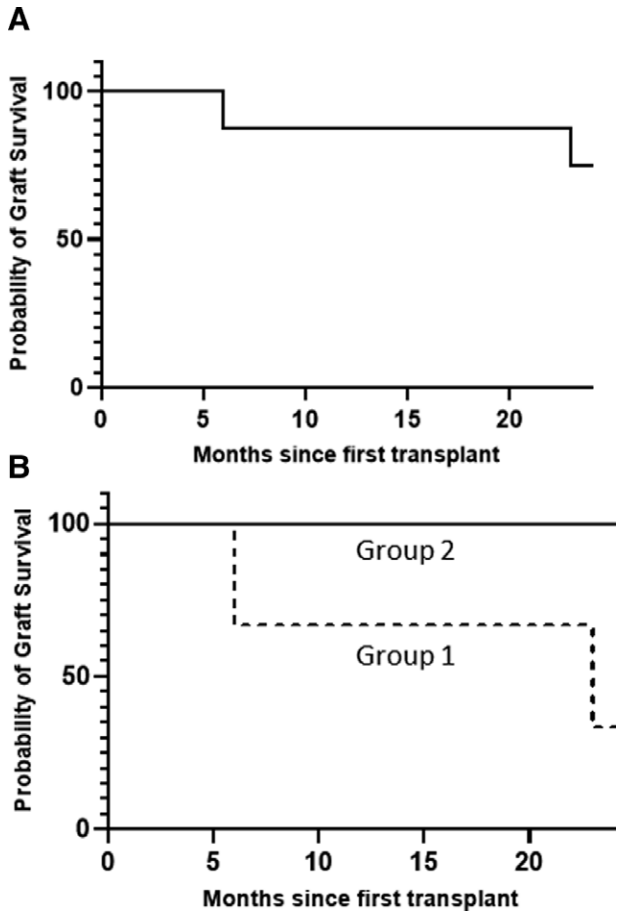

FIGURE 3. Probability of graft survival. A, Islet graft survival, defined as a basal or stimulated serum C-peptide level >0.3 ng/mL, is 87.5% and 75% at days 365 and 730, respectively. B, A comparison of the graft survival rate between groups 1 and 2 shows that while 100% of the patients in group 2 have graft function until day 730, in group 1, the graft survival rate is 66% on day 365 and 33% on day 730, with group 2 having a significantly higher graft survival rate than group 1 ($P = 0.004$).

induction immunosuppression with T-cell depletion and/or tumor necrosis factor alpha inhibition, and maintenance with both mechanistic targets of rapamycin and calcineurin inhibitors.[22] In our study, the fact that rapamycin was not used in maintenance immunotherapy may have contributed to the differences in results.

Differences in donor backgrounds should also be noted as factors that may influence transplant outcomes. We included patients with DCDs and DBDs. In islet transplantation, DCDs may provide clinically comparable transplantation results to those of DBDs[9,23]; however, in most of the reported clinical outcomes to date, transplantation has only been performed using DBDs. In a comparison of islet isolation results in Japan, there was a significant difference in islet yield between DCD and DBD, which may have an impact on transplantation outcomes.[24] Pancreatic allocation in Japan is unique as islet transplantation is classified as a tissue transplant and regulated differently from pancreatic transplantation, which is classified as an organ transplant and regulated by the Organ Transplant Law. Pancreases are mostly donated for solid pancreas transplantation but are donated for islet transplantation in donors with high BMIs or those who are elderly and brain-dead, DCDs, or when the pancreas is not donated for solid pancreas transplantation for any reason. Islet transplants from these donors have favorable outcomes in Japan, enabling donation without wasting the donated pancreas. However, the influence of donor factors on the lower insulin independence rate cannot be dismissed, warranting future examination of donor selection criteria.

Our trial demonstrated a manageable safety profile with no procedure-related bleeding events reported during percutaneous cannulation of the portal vein. In the CIT-07, procedure-related bleeding events occurred in 8.9% of percutaneous cannulation of the portal vein cases,[4] but none were reported in our study. In Japan, percutaneous transhepatic portal vein embolization is commonly performed before major hepatectomy,[25] possibly because radiologists are familiar with this technique. Although 3 SAEs related to neutropenia occurred, they were successfully managed without mortality or disability. It was unclear whether the neutropenia was due to immunosuppressive drugs, such as MMF or sulfamethoxazole-trimethoprim, or antiviral drugs used to prevent posttransplant infection; however, a reduction in the dose of these drugs resulted in improvement.

Despite the promising results of our trial, several challenges remain in islet transplantation. To address the shortage of donor organs, optimizing immunosuppressive regimens to balance efficacy and safety and refining patient selection criteria are ongoing. In particular, it is important to clarify the advantages of islet transplantation over insulin therapy, which has advanced in recent years, and to consider the criteria for patients indicated for transplantation. Of particular interest are the results of 1 study that was the first health economic study to compare islet transplantation with sensor-augmented pump therapy.[26] As insulin therapy advances, islet transplantation results,[27] and the indications for islet transplantation should be considered in light of advances in treatment results and healthcare systems in each country.

Additionally, long-term monitoring of graft function and metabolic outcomes is crucial for assessing the durability of the benefits of islet transplantation. In one study, islet transplantation resulted in the long-term achievement of glycemic targets in the absence of severe hypoglycemia in many recipients with T1D and impaired awareness of hypoglycemia.[28] The Edmonton group also reported that islet grafts function for 20 y[29] and that islet transplantation is expected to maintain long-term efficacy.

Our trial's limitation was low patient enrollment: 8 patients for 10 y across 7 centers, indicating limited experience. The division between IAK and ITA groups lacks significance due to the small sample size. Low activity levels question the proficiency of the center in islet isolation and transplantation, potentially impacting outcomes. Nonetheless, this trial led to insurance coverage for islet transplants in Japan and a rise in brain-dead donors, slightly increasing transplant numbers. The primary endpoint of the trial concerning the HbA1c value presented an issue. Initially, the JDS set the HbA1c level at 7.0%, making the study's primary endpoint an HbA1c (NGSP) level of 7.4%. However, the initial median HbA1c value was 7.3%, which may not have provided a sufficient baseline for improvement measurement. Despite this, the median HbA1c reached 6.3% by day 365, demonstrating significant progress and affirming the treatment's efficacy. This study showed that the limited number of islet transplants in Japan hinders the evaluation of treatment efficacy. To

TABLE 3.

Short Form 36 Health Survey

Measure	Visit	N	Mean (SD)	Median (range)
Physical functioning scale	Baseline	20	87.00 (13.32)	90.00 (50.00–100.00)
	Day 180	8	84.38 (11.48)	82.50 (70.00–100.00)
	Day 365	8	88.75 (9.54)	92.50 (75.00–100.00)
	Day 730	6	87.50 (7.58)	87.50 (75.00–95.00)
Role physical scale	Baseline	20	69.06 (23.69)	68.75 (18.75–100.00)
	Day 180	8	83.59 (18.28)	90.63 (50.00–100.00)
	Day 365	8	86.72 (20.17)	100.00 (50.00–100.00)
	Day 730	6	82.81 (9.38)	87.50 (62.50–100.00)
Role emotional scale	Baseline	20	74.17 (24.47)	75.00 (8.33–100.00)
	Day 180	8	91.67 (11.79)	95.83 (66.67–100.00)
	Day 365	8	81.25 (22.60)	91.67 (50.00–100.00)
	Day 730	6	88.69 (12.55)	91.67 (75.00–100.00)
Social functioning scale	Baseline	20	75.00 (22.94)	81.25 (37.50–100.00)
	Day 180	8	75.00 (20.04)	75.00 (50.00–100.00)
	Day 365	8	84.38 (19.76)	93.75 (50.00–100.00)
	Day 730	6	83.33 (20.41)	87.50 (50.00–100.00)
Mental health scale	Baseline	20	59.00 (27.94)	60.00 (0.00–100.00)
	Day 180	8	72.50 (14.39)	67.50 (55.00–95.00)
	Day 365	8	74.38 (19.72)	77.50 (45.00–100.00)
	Day 730	6	75.00 (19.24)	75.00 (40.00–95.00)
Pain scale	Baseline	20	72.90 (25.45)	69.00 (31.00–100.00)
	Day 180	8	69.00 (22.98)	67.00 (32.00–100.00)
	Day 365	8	75.00 (25.20)	78.00 (41.00–100.00)
	Day 730	6	71.00 (33.60)	81.00 (32.00–100.00)
Vitality scale	Baseline	20	47.19 (26.94)	50.00 (6.25–93.75)
	Day 180	8	55.47 (22.77)	53.13 (25.00–87.50)
	Day 365	8	57.81 (19.12)	53.13 (31.25–81.25)
	Day 730	6	63.54 (16.96)	68.75 (37.5–81.25)
General health scale	Baseline	20	43.25 (16.45)	43.50 (10.00–67.00)

TABLE 4.

Adverse event

Adverse event	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4	% (Grade 3 and 4)	% (Grade 4)
Neutropenia	5	0	0	2	1	37.5%	12.5%
Anemia	3	1	4	0	0	0%	0%
Thrombocytopenia	7	0	1	0	0	0%	0%
Insomnia	7	1	0	0	0	0%	0%
Headache	6	2	0	0	0	0%	0%
Oral ulcers	8	0	0	0	0	0%	0%
Diarrhea	5	2	1	0	0	0%	0%
Infection	8	0	0	0	0	0%	0%
Skin abnormalities	5	3	0	0	0	0%	0%
Edema	6	1	1	0	0	0%	0%
Liver dysfunction	2	6	0	0	0	0%	0%
Renal dysfunction	4	4	0	0	0	0%	0%
Hypertension	7	0	1	0	0	0%	0%
Hyperlipidemia	7	0	1	0	0	0%	0%
Ovarian cysts	8	0	0	0	0	0%	0%
Malignant neoplasms	8	0	0	0	0	0%	0%
Intra-abdominal bleeding	8	0	0	0	0	0%	0%
Complications related to regional anesthesia	8	0	0	0	0	0%	0%
Hepatic dysfunction and liver failure due to portal vein obstruction	8	0	0	0	0	0%	0%
Others	8	0	0	0	0	0%	0%

enhance future outcomes, it is crucial to address donor scarcity, reassess the donor allocation system, and ensure access to immunosuppressive medications comparable with those in other countries. Additionally, a thorough assessment of long-term outcomes is essential.

In conclusion, this trial provides valuable insights into the clinical efficacy and safety of islet transplantation in Japanese patients with T1D. By demonstrating improvements in glycemic control, reduction in the incidence of hypoglycemia, and maintenance of islet graft function, our study contributes to a growing body of evidence that supports the utility of islet transplantation as a therapeutic option for T1D. Addressing the remaining challenges and refining transplant protocols are essential to maximize the benefits of this promising therapeutic approach in clinical practice.

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