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Minireview

The Clinical Impact of Islet Transplantation

P. Fiorina[a,b], A. M. J. Shapiro[c], C. Ricordi[d] and A. Secchi[b,e,*]

[a] *Transplantation Research Center, Children's Hospital-Brigham and Women's Hospital/Harvard Medical School, Boston, MA*
[b] *Transplantation Medicine, San Raffaele Scientific Institute, Milan, Italy*
[c] *Islet Transplantation Center, Edmonton, Canada*
[d] *Diabetes Research Institute, Miami, FL*
[e] *Università Vita-Salute San Raffaele, Milan, Italy*
* *Corresponding author: Antonio Secchi, secchi.antonio@hsr.it*

Islet cell transplantation has recently emerged as one of the most promising therapeutic approaches to improving glycometabolic control in diabetic patients and, in many cases, achieving insulin independence. Unfortunately, many persistent flaws still prevent islet transplantation from becoming the gold standard treatment for type 1 diabetic patients. We review the state of the art of islet transplantation, outcomes, immunosuppression and—most important—the impact on patients' survival and long-term diabetic complications and eventual alternative options. Finally, we review the many problems in the field and the challenges to islet survival after transplantation. The rate of insulin independence 1 year after islet cell transplantation has significantly improved in recent years (60% at 1 year posttransplantation compared with 15% previously). Recent data indicate that restoration of insulin secretion after islet cell transplantation is associated with an improvement in quality of life, with a reduction in hypoglycemic episodes and potentially with a reduction in long-term diabetic complications. Once clinical islet transplantation has been successfully established, this treatment could even be offered to diabetic patients long before the onset of diabetic complications.

Key words: islet transplantation, type 1 diabetes mellitus, immunosuppression, late complications of diabetes.

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Introduction

The master treatment for patients affected by type 1 diabetes mellitus (T1D) is insulin therapy, which was a life-saving breakthrough when it was introduced. Insulin treatment cannot fully prevent chronic complications related to diabetes, and intensive insulin treatment increases the risk of fatal hypoglycemic episodes (1). Islet transplantation is a relatively new medical procedure to replace pancreatic function. Unfortunately, the lack of standardized protocols and the differences in inclusion criteria and in immunosuppressive regimens among studies have prevented islet transplantation from becoming the gold standard treatment for patients affected by T1D (2).

Indications for Islet Cell Transplantation

Frequent and severe hypoglycemic events are the most common indication for islet transplantation. Other possible indications include clinical and emotional problems associated with the use of exogenous insulin therapy that are so severe as to be incapacitating, and consistent failure of insulin-based management to prevent acute complications. On the other hand, islet after kidney (IAK) transplantation is restricted to patients with end-stage renal disease affected by T1D who underwent kidney transplantation alone or who rejected the pancreas after simultaneous kidney–pancreas (KP) transplantation; for islet transplant alone (ITA) selection of patients is an important issue. Currently the major problem with accurate indications is the absence of a controlled double-blind study showing the positive impact of islet transplantation on diabetic mortality and morbidity. Again, it is unclear whether the harmful toxic effects of immunosuppression can be recommended to type 1 diabetic patients, who can be treated with insulin-intensive treatment, insulin pump or even pancreas-alone transplant. In patients with a kidney graft, it is likely that islet transplantation will be acceptable, particularly in the absence of any change in the immunosuppressive regimen.

Metabolic Effects of Islet Transplantation

Islet full and partial function

According to the Cell Islet Transplantation Registry (CITR), which collected most of the North America Islet Centers data, the actual graft function (C-peptide >0.5 ng/mL) for IAK is almost 80% at 1000 days of followup. In the ITA group the actual graft function is almost 60% at 1000 days (Figure 1A).

There are several reports of islet cell transplantation achieving insulin independence and normalizing glucose

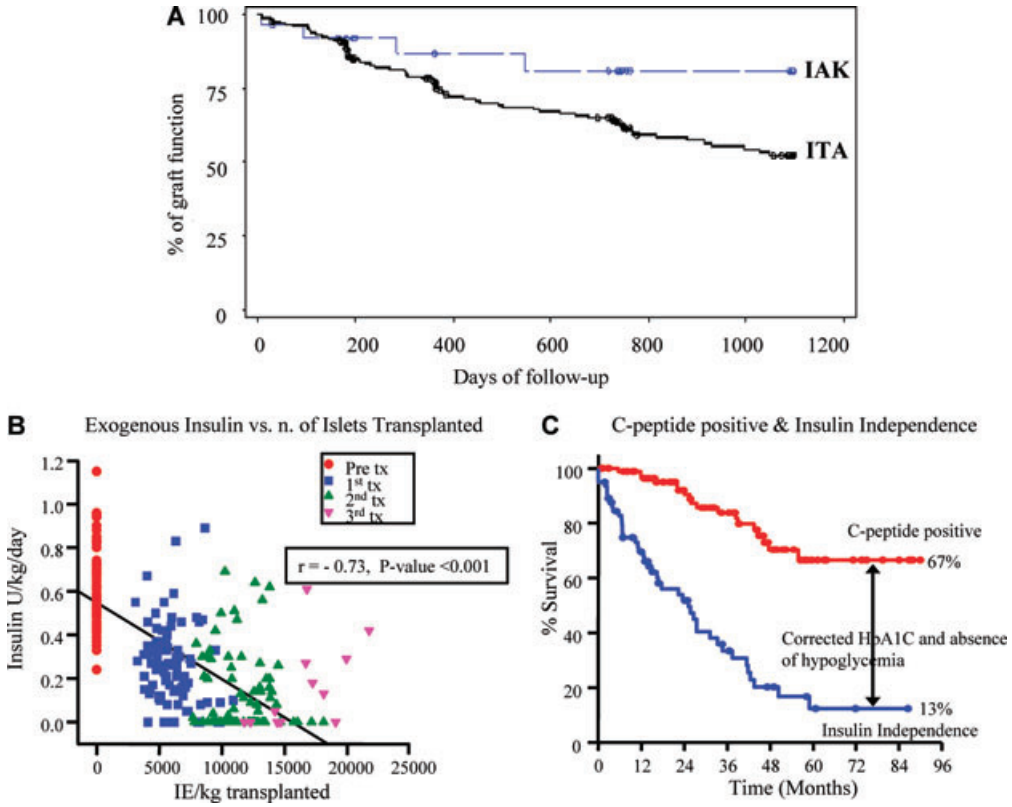

Figure 1: Graft survival according to C-peptide >0.5 ng/mL (data from the Collaborative Islet Transplantation Registry—CITR) (*Panel A*) in the islet after kidney (IAK) and in the islet transplant alone (ITA) groups. Daily exogenous insulin requirements are inversely related to islet mass (*Panel B*). The Edmonton experience in the ITA group: while only 13% of patients maintain insulin independence at 84 months, 67% of them showed a persistent C-peptide secretion with reduction of severe hypoglycemic episodes in the long term (*Panel C*).

homeostasis (3–5). The degree of metabolic compensation among patients with T1D who received an islet transplant is strictly correlated with the transplanted islet mass (Figure 1B, referring to Edmonton's experience). Unfortunately, few patients maintained insulin independence in the long term (3–5). However, despite the discrepancy between graft function and insulin independence (Figure 1C), most of the patients are capable of maintaining a sustained C-peptide secretion in the long term (Figure 2A) with a decrease in daily insulin unit (Figure 2B) and HbA1 c (Figure 2C), as shown by the CITR data.

In grafted patients, insulin is secreted intrahepatically and is cleaved by the liver, avoiding peripheral hyperinsulinemia and mimicking physiological insulin secretion (6). Luzi et al. showed that functioning islet grafts normalize basal hepatic glucose output, ameliorate insulin action and normalize plasma concentrations of amino acids (6). However, more than one donor pancreas is usually required to achieve insulin independence, suggesting impairment in graft function (6).

Among patients who experienced a loss of insulin independence, most achieved long-term partial islet function (with a C-peptide secretion >0.5 ng/mL). Despite the loss of insulin independence, patients showed a sustained C-peptide secretion in the long term (Figure 2A), associated with: a reduction in pretransplant insulin requirement of at least 50% (Figure 2B), a reduction of HbA1 c (Figure 2C) and a normal postabsorptive and insulin-mediated protein metabolism (7).

Hypoglycemia

Several studies confirm that intrahepatically transplanted islets respond appropriately to hypoglycemia and can prevent severe hypoglycemic episodes (Figure 1C, Edmonton's experience) (8). However, whether the abolishment of severe hypoglycemia is due to the reduction in exogenous insulin requirements or to the restoration of normal glucose counterregulation is a matter of active investigation (8).

Although either the ability to inhibit endogenous insulin secretion or the sympathoadrenal response during hypoglycemia is restored after islet transplantation (8), glucagon counterregulation is not completely corrected (8). It is not clear why intrahepatic islet transplantation does not restore hypoglycemic counterregulation or whether the loss

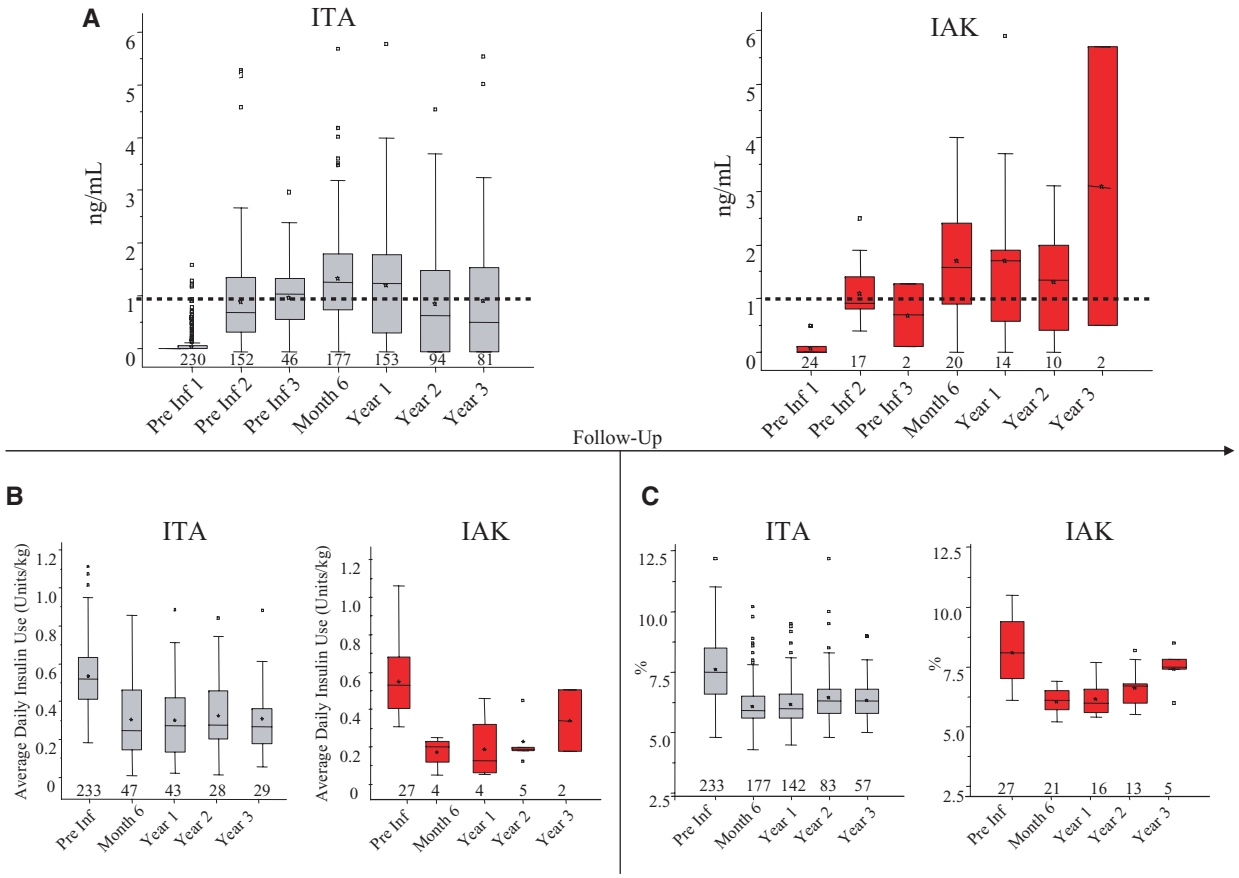

Figure 2: The Collaborative Islet Transplantation Registry (CITR) experience in islet after kidney transplantation (IAK) and islet transplant alone (ITA). Patients showed stable long-term C-peptide secretion (*Panel A*, dotted line represent the limit for full function), with a clear reduction in daily exogenous insulin use (*Panel B*) and reduction in HbA1c (*Panel C*) (adapted from CITR).

of symptom awareness is corrected by islet transplantation. Impairment in the neural activation of α-cells, a reduction in β-cell mass or an increase in hepatic clearance could account for this defective activation (8).

Lipid profile

While many papers have examined glucose metabolism, very few have dealt with lipid metabolism, and most of these have done so simply as a consequence of examining insulin sensitivity (7). A paper from 2001 showed that in a small group of patients who received islets after kidney transplants, either fully functioning or partially functioning islets improved lipid metabolism, with an evident reduction in lipid oxidation, contrary to the impairment in patients whose graft failed (7). All these patients were receiving immunosuppressive therapy for a previous kidney transplant, and most were receiving steroids.

A previous prospective study published in 2005 in *Diabetes Care* (9) showed the amelioration of abnormal lipid levels in the IAK group with partial function of the transplanted islets. In this study, triglyceride levels appeared lower in both KP and IAK groups, but not in the kidney-alone group (KD) group at 2 and 4 years. Mean total cholesterol levels were slightly but significantly increased from baseline in the KP and KD groups but not in the IAK group (9).

Unfortunately, patients with T1D who received an ITA tended to experience the new onset of hyperlypidemia, which can be moderate in some cases but can require statin treatment (10), due to the inclusion of rapamycin in the immunosuppressive protocol.

Effect of Islet Transplantation on Patient Survival

Few papers discuss the positive effect of islet transplantation on type 1 diabetic patients' morbidity and mortality. Unfortunately, these papers were not the result of clinical trials but were instead based on uncontrolled prospective or even retrospective studies; this seriously limits their general acceptance as proof-of-principle of the positive effect of islet transplantation.

One paper analyzed the effect of islet transplantation on patient survival (11). This work compared two populations of kidney-islet-transplanted patients: a successful group with C-peptide secretion > 0.5 ng/mL for more than 6 months and an unsuccessful group with early failure of the islet graft, who lost C-peptide secretion within 6 months of transplantation (11). All detailed studies before transplantation found that the two groups had similar general characteristics, metabolic status, immunosuppressive regimens, kidney graft function, degree of diabetic complications and major known cardiovascular risk factors. After 7 years of followup, the survival among patients in the group with successful islet transplantation and sustained restoration of β-cell function was significantly higher (90%) than among patients in the unsuccessful transplantation group (51%). This higher survival in the successful group was accompanied by higher C-peptide levels and lower insulin requirements compared to the unsuccessful group, despite similar glycated hemoglobin levels. The number of cardiovascular deaths (according to ICD-9) was higher in the group with unsuccessful transplants, who also had poorer atherosclerotic profile and endothelial function (11). This preliminary observation remains to be confirmed in controlled studies, possibly with a larger number of patients.

Effects of Islet Transplantation on Long-Term Diabetic Complications

Diabetes is a common disease characterized by chronic hyperglycemia and high morbidity and mortality (1). Large clinical trials have clearly shown that stringent glucose control can significantly reduce the risk of microvascular complications (1). However, intensive insulin treatment is associated with a threefold increase in severe hypoglycemia (1). So far, no controlled studies have clearly answered the question of whether islet transplantation can halt the progression of long-term diabetic complications. However, we must acknowledge the difficulties of performing large clinical trials, due to differences in islet isolation procedure, absence of standardized protocols and persistence of many regional-based immunosuppressive approaches.

A few uncontrolled preliminary studies from Milan, Miami and other groups have shown that the restoration of islet function is probably protective against long-term diabetic complications.

We must therefore critically appraise that most of the reported studies are uncontrolled, retrospective and frequently compare different eras and different cohort of patients. That being said we should appreciate the big effort from the Collaborative Islet Transplant registry (CITR) which is trying to organize data, immunosuppressive protocols and approaches from many North American islet transplant centers in a comprehensive way.

Islet transplantation and the heart

Islet transplantation has been shown to ameliorate diabetic cardiomyopathy in animal studies (12). Islet transplantation fully corrects the diabetes-induced changes in protein tyrosine phosphorylation in the myocardium of islet-transplanted mice (12). Thus, insulin delivered into the systemic circulation by pancreatic islets transplanted under the kidney capsule can correct altered heart insulin-signaling mechanisms in insulinopenic diabetes (12).

Few papers have addressed this issue in humans; a recent report indicated improvement in cardiovascular function over a 3-year follow-up period in kidney-transplant recipients with functioning islet transplant (11). Islet transplantation has been associated with an improvement in diastolic function and QT dispersion and a delay in intima media thickening (11). Furthermore, a reduction in atrial/ventricular natriuretic peptide, a marker of atrial and ventricular function, was evident during the followup period (11). The paper has many weaknesses (i.e. the small number of patients included and the bias of an uncontrolled study), but it has the strength of quantitative measurement (including parameters of systolic and diastolic function and atherosclerosis progression).

Islet transplantation and the vessels

Patients with type 1 diabetes are at high risk for macro-/microangiopathy (1). A previous report described the long-term beneficial effects of islet transplantation on micro- and macrovascular complications in 34 patients with T1D who received kidney transplants at a single institution. The authors found a reduction in carotid intima media thickness (IMT), an important index of eventual cardiovascular disease (11). The increased IMT in the groups with non-functioning islets reached values higher than those in the general population but similar to those in subjects with ischemic heart disease. Analysis of skin biopsies from islet-transplanted patients revealed that functioning islet transplants can induce positive micromodifications at the vessel level, such as an increase in the expression of von Willenbrand factor or endothelial nitric oxide (11), or can reduce the thickening of the capillary basement membrane, cellular swelling and the dilation of endoplasmic reticulum in endothelial cells (11). The small sample size and single-center data render this study interesting but not definitive.

Islet transplantation and the kidney

Nephropathy is one of the most common and serious complications of T1D (1). The Diabetes Control and Complications Trial demonstrated a reduced incidence of microalbuminuria in patients with type 1 diabetes who received intensive treatment rather than standard treatment (1). A 2003 paper in the *Journal of the American Society of Nephrology* showed that successful islet transplants in T1D patients with end-stage renal disease receiving kidney transplants help prolong graft survival and prevent

reduction in vascular function of the kidney graft (13). In another paper from the same group, noninvasive assessments of graft vascular function using the Doppler resistance index and microalbuminuria evaluations showed that patients with T1D who received a kidney transplant and an islet transplant showed better renal vascular function and cumulative kidney graft survival than the group without functioning islets (9,13).

The potential positive effect of islet transplantation on kidney function was confirmed by decreases in the urinary excretion of albumin, the urinary fractional excretion of sodium and the sodium excretion rate (13). The authors suggested that the restoration of endogenous C-peptide secretion may activate Na^+–K^+-ATPase in renal tubular cells or glomerular NO, thereby inducing an increase in sodium handling and a reduction in urinary sodium excretion (9,13).

There would be great benefit from a large study on the combined effect of islet transplantation and immunosuppression on kidney function, particularly now that some papers have shown nephrotoxicity in patients transplanted with islets alone (14).

Islet transplantation and the eyes

Diabetic retinopathy, the main cause of blindness in industrialized nations, is a potentially serious complication of all form of diabetes and is characterized by retinal neovascularization and sustained by different pathogenic mechanisms (15). Reduced retinal blood flow and accompanying hypoxia may occur before early signs of retinopathy. However, the relationship between early disturbances in blood flow and the onset of diabetic retinopathy remains controversial (15).

Little information is currently available on the effect of islet transplantation on diabetic retinopathy and the retinal microcirculation and the evolution of diabetic retinopathy.

A recent paper reported a statistically significant increase in retinal blood flow velocity at 1 year in patients with T1D who received islet transplants (16). The restoration of islet function can help control glucose excursion and, *per se*, can probably halt the alterations in retinal microcirculation. The Miami group reported a series of 12 patients who received islet transplants and were evaluated for the progression of diabetic retinopathy and neuropathy (17). Patients were examined by a single ophthalmologist and a single neurologist throughout the study period. All patients showed stabilization of their retinopathic disease after islet transplantation (17). Larger studies are required to confirm these preliminary reports.

Islet transplantation and the nervous system

Lee et al. assessed peripheral nerve function with a nerve conduction velocity (NCV) index (17) in islet-transplanted patients. Although no statistical analysis was provided, and the followup period was no longer than 2 years, the effect of β-cell replacement appeared to be positive on polyneuropathy. A preliminary report from the Milan group (18) showed, using the NCV index, that islet transplantation may induce long-lasting stabilization or even improvement of polyneuropathy in type 1 kidney-transplanted diabetic patients who also received a functioning islet transplant, reducing nerves' RAGE expression (18).

Alternative Approaches

Pancreas transplantation alone

Pancreas transplantation was the first step in the biological substitution of β-cell function in type 1 diabetic patients: the first pancreas transplantation was in 1966, and its 40th anniversary was celebrated in Minneapolis in December 2006. Pancreas transplantation is now an established clinical indication in type 1 diabetic patients also undergoing renal transplantation for end-stage renal disease: the simultaneous pancreas–kidney transplantation approach (SPK) (19). Recently, thanks to the refinement of technical approaches and improvements in immunosuppression strategies, pancreas transplant alone (PTA) has gained more favor among the experts (20). From 1966 to 2004, almost 20 000 SPK and around 1000 PTA pancreas transplants were performed worldwide (20). Graft survival has continued to improve. Comparing the 1987–1992 and 2001–2003 eras, pancreas survival improved from 76% to 85% in SPK and from 55% to 76% in PTA (19). The differences in graft survival rates for SPK and PTA were caused by a higher rate of graft loss due to rejection or thrombosis in the PTA group (21). With lower rates of technical and immunological failure, pancreas transplantation alone gained credence (22). Indications are history of frequent, acute and severe diabetic metabolic complications (hypoglycemia, hyperglycemia, ketoacidosis) requiring medical attention, incapacitating clinical and emotional problems with exogenous insulin therapy and the consistent failure of insulin-based management (23). The major concerns when proposing pancreas transplantation alone are surgical complications and the risk of vascular complications in patients already affected by advanced vascular disease. The continuation of this major risk through the perioperative period led to an important report suggesting that mortality among patients undergoing pancreas transplantation alone can be higher than among patients on the waiting list (24). On the other hand, pancreas transplantation, particularly recently, has been shown to halt the late complications of diabetes, namely cardiovascular disease, retinopathy and kidney dysfunction (25–27). Differences in results between pancreas and islet transplantations are presented in Table 1.

Artificial pancreas

Insulin pumps are pioneering attempts at creating an artificial pancreas. Since the first proposal of insulin pumps

Table 1: Effects of different approaches to substitute pancreatic function

	Islet transplantation	Pancreas alone	Insulin pumps
Surgery	Minor	Major	N/A
Relaparatomy	0%	30%	N/A
Rate of success	40–80%	50–80%	N/A
Function	Delayed	Immediate	Immediate
Insulin independence	Fragile	Stable	Absent
Impact on long-term diabetic complications	Possible	Proven	Likely but unproven
Hypoglycemic episodes	Unlikely	Few	Likely

N/A = not applicable.

in the late 1970s, their development progressed rapidly, with the creation of very precise, sophisticated miniaturized devices (28). The impact of these devices on blood glucose control is evident and has been shown in several studies (28). Nevertheless these results come at the cost of an increase in hypoglycemic episodes, which deeply affects the lifestyle and safety of patients (28). The development of natural pumps capable of releasing insulin depending on blood glucose levels will likely become the Holy Grail for the field. Progress has been made thanks to the development of glucose sensors, first available in 1999 (CGMS MiniMed) (29). Despite several efforts to close the loop, i.e. to have insulin released from the pump driven by a sensor, the availability of such an instrument does not seem imminent. The major limiting factor is its reliability, to avoid the risk of infusing insulin in hypoglycemia and to stop insulin infusion in hyperglycemia (29), which could be lethal in the absence of external controls. Finally, there has been no demonstration that an artificial pancreas can halt the progression of diabetic complications.

Encapsulated islets

The idea behind encapsulated islets is primarily avoiding antigen recognition and protecting islets from the immune response. The passage of small molecules (like insulin and glucose) but not of antibodies or large cells is one of the promises held by semipermeable membranes in islet encapsulation. This would effectively inhibit the destruction wrought by both humoral- and T-cell-mediated immunity.

Two patients with type 1 diabetes in Perugia, Italy, have been recently transplanted with encapsulated islets (30). The authors' extensive experimental background in the field enabled them to initiate a pilot clinical trial of the transplantation of microencapsulated human islets into nonimmunosuppressed patients with T1D (30). Their preliminary data showed that the procedure is safe and painless for the patient. Unfortunately, both patients remained on insulin therapy, but the improvement in glycated hemoglobin and the disappearance of hypoglycemia suggested that this is a path in need of further explanation (30).

New Immunological Strategies for Islet Transplantation

Several attempts have been made in order to achieve tolerance in islet-transplanted patients to avoid toxic immunosuppression. Human islet transplantation offers a unique setting in which to develop tolerogenic protocols. The failure of a tolerogenic protocol tested in islet transplantation will result in patients returning to insulin injections.

$CD34^+$ cells

Use of hematopoietic stem cells ($CD34^+$ cells) has been suggested as an interesting option for the islet transplantation field because of the induction of chimerism by $CD34^+$ for its immunosuppressive abilities. An ongoing trial at the University of Miami is using an immunosuppressive regimen combined with the infusion of donor hematopoietic stem cells ($CD34^+$ cells).

Efalizumab

Efalizumab is a blocking monoclonal antibody directed to LFA1, one of the most important integrins on lymphocytes, where it acts as an adhesion and costimulatory molecule (31). The use of anti-LFA1 in preclinical alloimmune and autoimmune models of islet transplantation has been shown to prolong islet transplantation (31). The efficacy of efalizumab is being evaluated as part of the immunosuppressive regimen in an ongoing trial at Emory University in Atlanta.

Anti-CD3-specific antibody

The use of anti-CD3 has been shown to induce tolerance in some nonautoimmune models of allograft transplantation (32) to reverse autoimmunity in NOD mice (33) and to slow the progression to permanent diabetes in humans with recent-onset diabetes (34). However, although treatment with anti-CD3 is efficient in nonautoimmune models, it has not been reported to enable long-term engraftment of allogenic islets in diabetic NOD mice. A new, humanized nonmitogenic version of OKT3 (HuOKT3γ1 Ala–Ala) has had promising results (35). It did not promote significant cytokine release when injected into mice with severe combined immunodeficiency (SCID) reconstituted with normal

human splenocytes. The University of Minnesota is testing the effect of treatment with HuOKT3γ1 induction in islet transplantation.

Antithymoglobulin (ATG)

Though ATG produced by rabbits immunized with human thymus has been on the market for the last 15 years, its mechanism of action was unknown. Preliminary observation suggested that ATG maybe superior to Daclizumab as far as 1 year's islet graft function (Paolo Fiorina, personal communication). This molecule has generated new interest now that ATG ability to expand antigen-specific regulatory T cells has been discovered (36).

Tipping the balance between regulatory and effector T cells

A very interesting approach that was recently proposed is based on the signaling by different cytokines between T-regs and T-effs (37). This approach was designed to block the IL15R antiapoptotic pathway in effector cells and to activate the IL2R pathways that promote apoptosis of T-effs and the activation of T-regs (37). According to this model, the use of an IL2 agonist and an IL15 antagonist combined with rapamycin permits long-term function in the very stringent model of allogenic islet transplantation (37).

Regulatory T cells and Rapamycin

There has been a growing recognition of the capability of regulatory T cells (Tregs) to tolerize antigen (Ag)-specific effector immune cells. Among the $CD4^+$ Tregs, the naturally occurring $CD25^+$ Tregs (nTregs)—originating from the thymus and constitutively expressing the transcription factor FOXP3—suppress both Ag-specific and Ag-nonspecific cellular immune responses, mainly *via* cell-cell contact. Tr1 cells—inducible Tregs generated by chronic exposure to Ag in the presence of IL-10 and defined by a unique cytokine production profile (*i.e.* IL-10^{++}, IL-5^+, TGF-b^+, IL-4^-)—suppress mostly Ag-specific immune responses, mainly *via* production of large amounts of IL-10 (38).

It is now well established that some immunosuppressive drugs interfere with the survival, expansion, and/or function of Tregs. On the contrary it was recently shown that Rapamycin is capable to elicit and expand these regulatory T-cells in the murine and human models, an action that is specific for Rapamycyn (mediated by mTOR) (39) and not observed with calcineurin inhibitors.

These observations pave the road to the development of clinical trials in islet transplantation based on regulatory T cells to induce immunetolerance, under a permissive immunosuppression with Rapamycin.

Table 2: Specific strategies to overcome obstacles to islet cell transplantation

Milestones	Strategies
Reduce toxic effects of hyperglycemia, islets' overwork and instant blood-mediated inflammatory reaction (IBMIR)	Oral hypoglycemic agents GLP-1 Long-acting insulin New heparin-like drugs
Alternative site for islet infusion	Bone marrow Skin Muscle Kidney
Protecting islet	GLP-1 Gene delivery
Targeting autoimmune response	B-cell depletion T-regs ATG
Targeting alloimmune response	Efalizumab PowerMix $CD34^+$ cells
Absence of revascularization	Endothelial progenitors cells VEGFR
Noninvasive monitoring of islet rejection/failure	HLA peptide Anti-GAD response MR/TC-PET imaging

Conclusions

Islet cell transplantation holds great promise for treating patients with T1D, given that it is a relatively noninvasive procedure and an attractive alternative to pancreas transplantation for restoring endogenous insulin secretion in patients with T1D (2).

Unfortunately, although some patients have excellent long-term survival, the success rate is much lower in terms of insulin independence or endogenous C-peptide secretion among other patients. Recent uncontrolled and preliminary studies have shown that this partial restoration of insulin and C-peptide secretion can be helpful and protective in long-term diabetic complications, but these results must be confirmed in larger studies.

Islet transplantation is therefore an extremely promising therapy, and while there are still significant barriers, like the development of anti-HLA antibodies, they do seem surmountable. The proof of concept for cellular replacement therapy in diabetes has been firmly established. It needs only to be improved and made more widely available to the millions of desperate patients with T1D who search for alternatives to a life of insulin injections, hypoglycemia and the risks of end-organ damage (Table 2).

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