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Beta Cell Function After Islet Transplantation

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1. Introduction

1.1. Islet cell transplantation for type 1 diabetes

The transplantation of pancreatic islets of Langerhans is a promising treatment for “brittle” type 1 diabetics, because it is a minimally invasive procedure that replenishes the beta cell mass lost due to autoimmunity. This procedure also provides an opportunity for a “cure” from diabetes based on the achievement of freedom from dependence on exogenous insulin and severe hypoglycemic events. Although islet transplants had been attempted for several decades, they achieved minimum success in terms of post-transplant graft function. The publication of the Edmonton Protocol [1] documenting consistent achievement of insulin independence after islet transplantation, has led to a dramatic increase not only in the number of procedures performed worldwide but also in other related areas in the field of islet transplantation. Breakthroughs have been made in the area of pancreas procurement and preservation with study into ductal preservation, the two layer method, and the type of preservation solution used. Furthermore, there has been much progress in the islet isolation process by bringing standards up to cGMP qualifications, optimization of collagenase enzymes, and using iodixanol for continuous density gradient purification [2]. Some of the hurdles facing further success in this treatment are:

- i. lack of suitable donor pancreases;
- ii. difficulties in isolating high quality islets on a consistent basis;
- iii. improving the engraftment of transplanted islets;
- iv. development of an islet-friendly immunosuppression and
- v. improving long-term survival of transplanted islets.

1.2. Post-transplant outcome

According to a recent report from the Collaborative Islet Transplant Registry, 677 patients have received either an islet transplant alone (ITA) or islets-after-kidney (IAK) transplants [3]. There has been a remarkable improvement in the post-transplant graft function in recent times. Prior to the publication of Edmonton protocol, the achievement of insulin-independent status by islet transplant recipients was <10%. Patients treated initially under the Edmonton protocol showed remarkable achievement of 82% insulin-independent status at one year post-transplant. However, this result proved to be unsustainable when the five year insulin-independence rates fell to 12.5% at the same center [4]. This data resulted in skepticism on the use of allogeneic islet transplantation as a reliable treatment for long-term success. With the introduction of thymoglobulin at induction phase and the combination of prograf, rapamycin and/or mycophenolate mofetil as maintenance immunosuppressive agents, the islet transplant survival rate has significantly improved to 50% at five year post-transplant [5]. Control of inflammatory reaction during peri-transplant period with the use of TNF- α blockers also played a key role in this improvement. These remarkable results necessitated comparison with whole pancreas transplantation which is considered as an established clinical procedure. Although whole organ treatment achieved high levels of graft survival in the years 1994-1997, the islet survival rate at five years has reached around fifty percent in 2010-2011, comparable to the level of whole pancreas graft success [5]. Moreover, islet cell transplantation seems to confer significantly better glycemic control than maximal medical therapy, and essentially eliminates hypoglycemic unawareness. These results have brought back the enthusiasm in this field.

2. Molecular mechanism of beta cell dysfunction

2.1. Early events after islet transplantation

The liver is the most commonly used site for transplantation of islets. Data supporting the use of this transplant site came from autologous islet transplants in patients with chronic pancreatitis, which showed that islets can function inside the liver for several years. There are several drawbacks associated with the liver as a host site for islets. Major factors affecting islet function include hypoxia, drug toxicity and instant blood-mediated inflammatory reaction (IBMIR). Together, these events may lead to loss of up to 75% of islet transplant mass. IBMIR is primarily a response of innate immune system to isolated islets. Major characteristics of IBMIR include activation of coagulation and complement cascades and infiltration of inflammatory cells. Several approaches are adopted to minimize the deleterious effects of IBMIR which include infusion of low molecular weight dextran sulfate and also inclusion of anti-inflammatory molecules during the infusion of islets. Besides the innate immune response, islets transplanted into liver may experience low oxygen tension. Activation of resident Kupffer cells may pose additional risk to islet survival. In addition, high concentrations of immunosuppressive drugs in the portal vein are likely to exert toxic effect on the transplanted islet mass [6].

2.2. Alloimmunity

The exposure of body to allogeneic tissues via organ/cell transplantation, blood transfusions, pregnancy can cause development of anti-human leukocyte antigen (HLA) antibodies [7]. These *de novo* HLA antibodies have been shown to play a significant role in the early graft loss after solid organ transplantation [8]. Currently, HLA matching between the recipients and donors is not performed before islet cell transplantation. Moreover, to achieve and/or maintain insulin independence and good metabolic control in an islet recipient, multiple islet infusions from multiple donors and high doses of immunosuppressants are generally required. The requirement of multi-donor infusions and reduction or weaning of immunosuppressants due to significant adverse effects could cause patients eventually to develop HLA antibodies against islet graft.

The issue of sensitization of alloantigens after islet cell transplantation has been raised by the Edmonton group in 2007 [9]. 98 islet transplant recipients were screened for HLA antibodies by flow-based methods. Twenty-nine patients (31%) represented *de novo* donor specific antibodies following islet transplantation. Among 14 recipients who discontinued immunosuppression, 10 recipients (71%) were largely sensitized with panel reactive antibody $\geq 50\%$. On the other hand, only 11 of 69 (16%) recipients who continued immunosuppression became broadly sensitized posttransplant. This study suggested that development of HLA antibodies after islet transplantation is concerning and withdrawal of immunosuppression completely following failed islet transplantation raises the risk for broad sensitization. Along with the report of Edmonton group, there are several studies that have demonstrated that islet alone transplant recipients develop donor-specific and/or nondonor-specific HLA antibodies, especially following discontinuation of immunosuppression [10-13].

In contrast, in the report of Geneva group it was shown that multiple islet infusions did not act as a risk factor for appearance of anti-HLA antibodies [14]. The group claimed that transplantation of islets in liver might cause less immunogenicity. After combined kidney-islet transplantation and continued immunosuppression even with failed islet graft function, patients had a low risk for sensitization as long as their kidney remained functional.

It has been known that islets express mainly HLA class I antigens on their surfaces. Previous reports demonstrated that patients develop antibodies posttransplant not only against HLA class I antigens, but also against HLA class II antigens [9]. Jackson et al. showed that there would be an induction of HLA class II expression on human islets under inflammatory conditions, which in return may be a possible cause of allosensitization [15]. For this aim, the group conducted an experiment in which they had two groups of isolated human islets; group 1 was control group and cultured at 37°C, whereas group 2 was cultured in the same condition and treated with tumor necrosis factor alpha (TNF- α) and interferon gamma (INF- γ). Presence of HLA class II on islet surface was analyzed by real-time polymerase chain reaction (PCR), immunofluorescence and flow cytometry. Expression of class II transactivator, HLA-DR- α and HLA-DR- β 1 increased maximum 9.38, 18.95 and 46.5 fold respectively in group 2 compared to control group after 24 hours of incubation with TNF- α and INF- γ which is shown by real-time PCR analysis. Fluorescent imaging and flow cytometric analysis confirmed the significant increase in the expression of HLA class II expression both on

islet α and β cells after cytokine treatment. Inflammatory conditions shortly after islet transplantation up-regulates HLA class II antigens on islet surfaces that trigger alloimmunity. Thus, protocols which provide adequate and efficient control of inflammation after islet transplantation should be considered to improve islet transplant outcome.

Collaborative Islet Transplant Registry reported the sensitization rates against HLA class I antigens pre- and posttransplant in islet alone recipients in 2011 [16]. Data is collected from 303 islet alone recipients between January 1999 and December 2008. Panel reactive antibody (PRA) pretransplant and PRA at 6 months and yearly posttransplant correlated to measures of islet graft failure. Pretransplant PRA showed not to be a predictor of islet graft failure; whereas there was 3.6 fold increased hazard ratio for graft failure when the recipient developed PRA $\geq 20\%$ post-transplant. Each additional islet infusion increased the cumulative number of mismatched HLA alleles from a median of 3 to 9; respectively for one infusion and for 3 infusions. Significantly higher rate of PRA $\geq 20\%$ was observed in recipients who had complete graft loss with discontinued immunosuppression compared to recipients who had functioning grafts with continuing immunosuppression. Development of *de novo* HLA class I antibodies is less pronounced in recipients with exposure to repeat HLA class I mismatched than increased class I mismatch. Reducing the number of islet donors used for each patient and repeating HLA I mismatches with consequent islet transplantation without presence of donor specific anti-HLA antibodies are vital factors to decrease the risk of allosensitization.

Currently, there is no clearly defined monitoring tool for alloimmunity in islet cell transplantation, but researchers have proposed many experimental tools to assess alloreactivity in islet transplanted patients. Alloantibodies, soluble CD30 level, cytotoxic lymphocyte gene expression and microparticles in peripheral blood are the markers which were shown to detect allogeneic rejection after islet transplantation. Monitoring panel reactive antibody in immunosuppressed recipients had little clinical value to assess islet graft survival [16, 17].

Team	Approach	Outcome	References
Edmonton group	Alloantibodies	Pretransplant HLA antibodies reduce graft survival after islet transplantation.	[9]
CITR report	Alloantibodies	Monitoring PRA in immunosuppressed patients had little clinical value for islet graft survival.	[16]
Minnesota group	Soluble CD30	No correlation between sCD30 levels and graft function at 1 year was found. A greater reduction in sCD30 levels posttransplant was associated with full graft function.	[18]
Miami group	Cytotoxic lymphocyte (CL) gene expression	Increased CL gene levels could predict islet allograft loss.	[19]
GRAGIL group	Microparticles	MPs and C-peptide showed opposite pattern. MPs levels in peripheral blood increase with acute rejection of islet allograft.	[20]

Table 1. Immunologic tools to assess alloimmunity after islet cell transplantation

Soluble CD30 (sCD30) is a cell membrane protein of tumor necrosis factor receptor family. sCD30 is released into blood with the activation of CD30 + T cells, leading to speculation that it may act as a marker for immune system activation [21]. Although it has been shown to be predictive for acute rejection in lung, kidney, and heart transplantation [22-24], there are not many reports about the role of sCD30 in the prediction of early graft loss following islet transplantation. In the study of Hire et al., 19 allograft islet recipients treated with three different immunosuppression inductions were evaluated retrospectively for the serum sCD30 levels [18]. Pretransplant, early posttransplant day (day 4-7), one month posttransplant, late posttransplant (day 90-120) sCD30 levels were measured and correlated with islet graft outcomes at 1 year. No correlation between sCD30 levels at any time point and graft function at 1 year was found. However, a greater reduction in sCD30 levels posttransplant was associated with full graft function. Therefore, sCD30 may be of value for immune monitoring of islet allografts.

Cytotoxic lymphocyte (CL) genes granzyme, Fas ligand and perforin may play an active role in the course of acute allograft rejection. University of Miami group studied 13 islet transplant recipients treated with steroid-free immunosuppressive regimen in order to demonstrate whether CL gene expression could be a predictor of allogeneic rejection [19]. All patients attained insulin independence; however, 8 of them restarted insulin therapy. Real-time PCR was used to assess CL gene mRNA levels. The group demonstrated that recipients who restarted insulin therapy had a significant elevation of CL gene mRNA levels and the most reliable measure of ongoing graft loss was granzyme B. Hence, increased blood CL gene levels might be a potential marker to predict islet allograft loss.

Microparticles (MP) are plasma membrane fragments of apoptotic cells in peripheral blood. The quantity of microparticles is correlated with the degree of cell death, so they are considered to be indicators of apoptosis. Kessler et al. demonstrated the elevation of microparticles in peripheral blood at the time of acute rejection following intraportal islet transplantation with a case report [25]. Loss of islet graft function without the presence of GAD65, IA2 or anti-HLA antibodies brought up the diagnosis of acute cellular rejection. With a successful steroid bolus therapy, MPs level declined and the patient regained islet function. In 2011, Toti et al. [20] demonstrated from three islet transplant recipients that in the case of rejection, C-peptide and MPs levels exhibited opposite pattern and a decline in C-peptide was related with increased insulin needs. This data suggested an increment in MPs level might indicate allogeneic rejection. Thus, MPs level in peripheral blood might be a useful tool to monitor allogeneic rejection after islet transplantation.

2.3. Autoimmune recurrence

Type 1 diabetes is an autoimmune disease in which pancreatic beta cells are destroyed through a T-cell mediated mechanism in genetically susceptible individuals [26]. Autoantibodies against pancreatic islets comprise anti-glutamate decarboxylase 65 (GAD65), islet cell autoantibody (ICA), anti-insulin autoantibody (IAA), anti-tyrosine phosphatase autoantibody (IA-2) and against zinc transporter ZnT8. Antibodies present in serum against these pancreatic islet antigens are commonly used to predict and or diagnose the disease in clini-

cal practice. For successful islet cell replacement, it is crucial to prevent recurrent destruction of beta cells through existing autoimmune destruction. The graft failure due to recurrent autoimmunity in a pancreas segment transplanted between identical twins was proven with the demonstration of insulinitis in the transplanted tissue [27]. Islet specific T cells seem to have a basic role in the process of autoimmune destruction of beta cells [28].

To investigate T-cell allo- and autoreactivities in peripheral blood following islet transplantation, Roep et al. examined 7 islet allograft recipients [29]. They showed that three patients who got thymoglobulin for induction immunosuppression and retained full islet function for more than 1 year exhibited minor autoreactivities but no alloreactivities. Three patients who did not get thymoglobulin had rapid decline (<3 weeks) in islet function and showed alloreactivities; but one out of these three patients had rapid increase in autoreactivity to several islet autoantigens prior to alloreactivity. One recipient who did not receive thymoglobulin exhibited hyperautoreactivity with no detectable alloreactivity and developed delayed loss of islet graft function consequently (<33 weeks); which indicated that autoimmune recurrence might be the cause of chronic islet graft dysfunction. In this study, because of the excellent outcomes in thymoglobulin group, the authors evaluated allo- and autoimmunity again in a bigger sample sized group in 2008 [30]. 21 islet recipients under thymoglobulin induction and tacrolimus plus mycophenolate mofetil maintenance immunosuppressive regimen were studied. Immunity against allo- and autoantigens were checked at pretransplant and at 1 year posttransplant. The analyses showed that existence of cellular autoimmunity pretransplant and posttransplant was related with delayed insulin independence and lower levels of circulating C-peptide during the first year posttransplant. Seven out of eight patients with no previous T-cell autoreactivity achieved insulin independence; whereas none of the four patients with autoantibodies against GAD and IA-2 before transplantation became insulin independent. Cellular alloreactivity and autoantibody levels did not show significant involvement with the outcome. Based on these findings, the authors commented that thymoglobulin may cope sufficiently with alloimmunity, but insufficient to control islet autoreactivity in an early period. The issue of autoimmunity remains unaddressed and needs further investigation.

Team	Approach	Outcome	References
Roep <i>et al.</i>	Autoantibodies	Autoantibodies increased due to autoimmune activity, but did not indicate loss of graft function.	[29]
Roep <i>et al.</i>	T-cell autoreactivity in peripheral blood	Pre- and posttransplant cellular autoimmunity were associated with delayed insulin independence. Autoantibody levels did not affect islet allograft outcome.	[30]
Matsumoto <i>et al.</i>	GAD65 specific global immune assay	Broad repertoire of islet antigen-specific T cells secreting various cytokines were related with chronic graft failure.	[31]

Table 2. Immunologic tools to assess autoimmunity after islet cell transplantation

Autoimmunity recurrence might be assessed by monitoring islet specific autoantibodies and T-cell autoreactivity. But the association between autoantibodies and insulin independence and islet graft outcome are variable; increase in autoantibody levels were shown due to autoimmune activity but did not indicate loss of islet graft function [29, 32]. Assays that measure anti-islet cellular autoimmunity before and after islet transplantation demonstrated that pre-and posttransplant cellular autoimmunity were related with delayed insulin independence and lower levels of circulating C-peptide during the first year posttransplant [30]. Nonetheless, in this study islet allograft outcome did not seem to be affected by autoantibody levels or cellular alloreactivity.

Matsumoto et al. have reported on a global immune assay specific for GAD65 (EpiMax) in order to analyze the property of autoreactive T-cell responses [31]. Five type 1 diabetic patients were studied 1 year after allogeneic islet transplantation. All patients achieved insulin independence at 1 year. Three out of five patients maintained long-term insulin independence and EpiMax affirmed minimum T-cell responses in these patients. In contrast, the two patients who developed chronic graft failure and lost insulin independence showed broad repertoire of GAD65 specific T-cells secreting various types of cytokines, including IL-5, IL-13, IL-17, TNF- α , and IFN- γ . In addition to those observations, IFN- γ and IL-13 expressing CD4⁺ T cells and IFN- γ expressing CD8⁺ T cells were encountered in the other two failed patients. These findings suggested that broad repertoire of islet antigen-specific T cells which secrete variable types of cytokines were related with chronic graft failure, preventing islet recipients from maintaining long-term insulin independence.

Immunosuppression

Following transplantation of islets, administration of immunosuppression is essential to maintain graft function. However, most of the immunosuppressive drugs also have adverse effects on beta cell function. Careful selection of immunosuppressive regimen is critical for prolonged function of transplanted islets.

2.3.1. Early period of islet cell transplantation

Corticosteroid was a widely used agent as maintenance immunosuppression in the pioneering days of islet cell transplantation in 1990's (Table 3). During this decade, majority of islet cell transplants were after or performed simultaneously with kidney transplantation. Corticosteroid has antiinflammatory as well as immunosuppressive effects by direct or indirect actions on various leukocytes, including T lymphocytes, monocytes and macrophages, through glucocorticoid receptor [33, 34]. However, steroid therapy leads to β cell dysfunction and insulin resistance. [35, 36] Deterioration of insulin secretion from β cell by steroid treatment has been reported, caused by enhanced α -adrenergic receptor signaling [37], β cell apoptosis [38] and activated K⁺ channel [39]. Insulin resistance in liver, adipose tissue and skeletal muscle by long-term steroid administration are well known clinically and in basic studies [40-42]. Thus, steroid use for the purpose of maintenance immunosuppression has been averted in the recent decade of islet transplantation (Table 3).

The calcineurin inhibitors (CNIs) have been major players in maintenance immunosuppression of islet cell transplantation. Cyclosporine A and tacrolimus are currently available CNIs in clinic. They inhibit calcineurin, a serine-threonine phosphatase, which is responsible for dephosphorylation of nuclear factor for activated T cells (NF-AT), which in turn results in inactivation of the transcription of cytokine genes. However, CNIs might have β cell toxicity since calcineurin is expressed in β cell and regulates β cell growth as well as function [43, 44].

Azathioprine is a purine analog, serving as a blocker of de novo pathway in purine synthesis in actively proliferative cells such as T cells and B cells [45]. Currently this drug is used for immunosuppression in allogeneic transplantation and autoimmune disease like rheumatoid arthritis as well as therapy in hematologic malignancies [46]. Azathioprine may also prevent the onset of diabetes [47, 48] and no major β cell toxicity of azathioprine has been reported.

2.3.2. Edmonton protocol

Remarkable success in islet transplant survival was achieved by the University of Alberta group using steroid-free immunosuppression regimen that included daclizumab, tacrolimus and sirolimus, resulting in that all 7 recipients achieving insulin independence [1]. The benefit of Edmonton protocol is to eliminate the risk of steroid-induced β cell toxicity as well as insulin resistance and increasing the dose of transplanted islets. However, the protocol uses tacrolimus that has the effect of β cell deterioration.

Publication year	Pts no.	Induction therapy	Maintenance therapy			Transplant type	Donor no.*	Major outcomes	Refs
			Steroid	CNIs	Other				
1990	9			✓ Tac		Islet after liver transplant	M/S	5 pts achieved II	[49]
1991	3		✓ Pred	✓ CsA	✓ Aza	ITA	M/S	Rejected 2 weeks after ITA	[50]
	3	✓ mALG	✓ Pred	✓ CsA	✓ Aza	IAK	S	Partial function**	
	3	✓ mALG	✓ Pred	✓ CsA	✓ Aza	IAK	M	II for 7, 14 and 121 days	
1991	4	✓ ATG (3 pts)	✓ Pred	✓ CsA	✓ Aza	IAK	M/S	1 pt achieved II	[51]
	2	✓ ATG	✓ Pred	✓ CsA	✓ Aza	SIK	M/S		
1992	10			✓ Tac		Simultaneous Islet-Liver transplant	S	6 pts achieved II	[52]

Publication year	Pts no.	Induction therapy	Maintenance therapy			Transplant type	Donor no.*	Major outcomes	Refs
			✓Pred	✓Tac	Other				
	4		✓Pred	✓Tac		Simultaneous Islet-Liver transplant	S	Partial function**	
	7		✓Pred	✓Tac		SIK	M	Partial function**	
1993	2	✓mALG ✓15-DSG	✓Pred	✓CsA	✓Aza	SIK	S	1 pt achieved II	[53]
1997	6		✓mPred	✓Tac		Simultaneous Islet-Liver-Bone marrow transplant	S	3 pts achieved II	[54]
1997	8	✓OKT3	✓mPred	✓CsA	✓Aza	IAK (7 pts) or SIK (1 pt)	M/S	2 pts achieved II	[55]
1997	20	✓ATG	✓Pred	✓CsA	✓Aza	IAK (7 pts) or SIK (13 pt)	M/S	7 pts achieved II	[56]
1997	3	✓ATG	✓Pred	✓CsA	✓MMF	SIK (2 pts) or IAK (1 pt)	M/S	Partial function**	[57]
1998	7	✓ATG (3pts)	✓Pred	✓CsA	✓Aza	IAK	M	2 pts achieved II	[58]
1999	12	✓ATG	✓Pred	✓CsA	✓Aza	IAK (12 pts) or SIK (12pts)	M/S	Partial function**	[59]

Table 3. Immunosuppression protocols in clinical islet transplants published in 1990's. *M: Multiple donor transplants, S: Single donor transplant. ** Not achieved II, but positive C-peptide or decreased insulin requirement was confirmed. Abbreviations; 15-DSG: 15-deoxyspergualin, ATG: antithymocyte globulin, Aza: azathioprine, CNIs: Calcineurin inhibitors, CsA: Cyclosporine A, IAK: Islet after kidney transplantation, II: Insulin Independence, ITA: Islet transplantation alone, mALG: Minnesota antilymphoblast globulin, MMF: mycophenolic mofetil, mPred: methylprednisolone, Pred: Prednisone, SIK: Simultaneous islet kidney transplantation, Tac: Tacrolimus.

Publication year	Pts no.	Induction therapy	Maintenance therapy			Transplant type	Donor no.*	Major outcomes	Refs
			Steroid	CNIs	Other				
2000	13	✓ATG or ✓Bas	✓Pred	✓CsA	✓Aza or ✓MMF	SIK, IAK or Islet after lung transplant	M/S	2 pts achieved II	[60]
2000	7	✓Dac		✓Tac	✓Sir	ITA	M	100% II	[1]
2001	2	✓ATG or ✓Bas	✓Pred	✓CsA	✓MMF	SIK (5 pts) or IAK (2 pts)	M/S	Partial function**	[61]

Publication year	Pts no.	Induction therapy	Maintenance therapy		Transplant type	Donor no.*	Major outcomes	Refs	
2001	10	✓Bas	✓Pred	✓CsA	✓MMF	IAK	M/S	2 pts achieved II	[62]
2003	6	✓Dac		✓Tac	✓Sir	ITA	M/S	3 pts achieved II	[63]
2004	6	✓OKT3γ1		✓Tac	✓Sir	ITA	S	4 pts achieved II	[64]
2004	13	✓Dac		✓Tac	✓Sir	ITA (9 pts) or IAK (4 pts)	M	11 pts achieved II	[65]
2004	10	✓Dac		✓Tac	✓Sir	ITA	M/S	5 pts achieved II	[66]
2004	6	✓Dac		✓Tac	✓Sir	SIK	M	5 pts achieved II	[67]
2005	8	✓ATG ✓Dac ✓Eta		✓Tac	✓MMF ✓Sir	ITA	S	100% II after single infusion	[68]
2005	16	✓Dac ✓Inf (8pts)		✓Tac	✓Sir	ITA	M/S	14 pts achieved II	[69]
2005	22	✓Dac/ ✓Bas		✓Tac/ ✓CsA	✓Sir/ ✓Eve	IAK or ITA	M/S	15 pts achieved II	[70]
2005	65	✓Dac		✓Tac	✓Sir	ITA	M/S	44 pts achieved II	[4]
2005	10	✓ATG or ✓Bas		✓Tac	✓Sir or ✓MMF	ITA	M/S	100% II	[71]
2006	8	✓Dac		✓Tac	✓Sir	IAK	M/S	100% II	[72]
2006	6	✓Dac		✓Tac	✓Sir	ITA	M	3 pts achieved II	[73]
2006	36	✓Dac		✓Tac	✓Sir	ITA	M/S	16 pts achieved II	[74]
2007	11	✓Dac		✓Tac	✓Sir or ✓MMF plus ✓Exe		M/S	8 pts achieved II	[75]
2007	10	✓Dac		✓Tac	✓Sir	ITA	M/S	6 pts achieved II	[76]
2007	19	✓Dac		✓Tac	✓Sir or ✓MMF	ITA	M/S	16 pts achieved II	[77]

Publication year	Pts no.	Induction therapy	Maintenance therapy	Transplant type	Donor no.*	Major outcomes	Refs
2008	5	✓ATG	✓Tac ✓Sir	ITA	M	3 pts achieved II	[78]
	5	✓ATG		ITA	M	Partial function**	
2008	13	✓Dac	✓Tac ✓Sir	SIK	M/S	7 pts achieved II	[79]
2008	7	✓Dac ✓Inf ✓Eta	✓Pred (2 pts) or mPred (1 pt) ✓Tac	✓Sir ✓MMF (2 pts) IAK	M/S	6 pts achieved II	[80]
2008	6	✓ATG ✓Eta	✓CyA	✓Eve →MMF ITA	M/S	5 pts achieved II	[81]
2008	4	✓Dac	✓Tac ✓Sir	ITA	M	100% II	[82]
	6	✓Dac ✓Eta	✓Tac	✓Sir ✓Exe ITA	M/S	100% II	
2008	3	✓Ale	✓Tac	✓Sir ✓MPA ITA	M/S	2 pts achieved II	[83]
2008	6	✓Dac ✓Inf	✓Tac	✓Sir Islet transplant with Bone marrow	S	3 pts achieved II	[84]
2009	14	✓Dac	✓Tac ✓Sir	ITA	M	100% II	[85]
2009	15	✓Dac or ✓Bas	✓Tac ✓Sir	IAK	M/S	100 pts achieved II	[86]
2010	8	✓ATG		✓Sir ✓MMF ✓Efa ITA	M/S	100% II	[87]
2010	8	✓Dac	✓Tac	✓Sir ITA	M/S	100% II	[88]
	4	✓Dac	✓Tac	✓Sir ✓Efa ITA	S	100% II after single infusion	
2010	5	✓ATG ✓Bela		✓Sir or ✓MMF ITA	M/S	100% II after single infusion	[89]
	5	✓ATG ✓Efa		✓Sir or ✓MMF ITA	M/S	100% II after single infusion	
2011	3	✓ATG ✓Eta ✓Ana	✓Tac	✓MMF ITA	M/S	100% II after single infusion	[90]
	3	✓Dac	✓Tac	✓Sir ITA	M	100% II	

Publi- cation year	Pts no.	Induction therapy	Maintenance therapy	Transplant type	Donor no.*	Major outcomes	Refs
2011	4			ITA**	M/S	Partial function***	[91]

Table 4. Immunosuppression protocols in clinical islet transplants published after 2000. *M: Multiple donor transplants, S: Single donor transplant. **Microencapsulated islets transplanted. *** Not achieved II, but positive C-peptide or decreased insulin requirement was confirmed. Abbreviations; Ale: Alemtuzumab, ATG: antithymocyte globulin, Aza: azathioprine, Ana: anakinra, Bas: basiliximab, Bela: belatacept, CNIs: Calcineurin inhibitors, CsA: Cyclosporine A, Dac: daclizumab, Efa: efalizumab, Eta: etanercept, Eve: everolimus, Exe: exenatide, IAK: islet after kidney transplantation, II: insulin independence, Inf: infliximab, ITA: islet transplantation alone, mALG: Minnesota antilymphoblast globulin, MMF: mycophenolic mofetil, MPA: mycophenolic acid, mPred: methylprednisolone, Pred: prednisone, SIK: simultaneous islet kidney transplantation, Sir: sirolimus, Tac: tacrolimus

Sirolimus is an inhibitor of mammalian target of rapamycin (mTOR), which plays an important role in cell cycle from late G1 to S phase in T cells [92]. The effect of sirolimus in β cell function is still unclear; impaired β cell proliferation and islet graft function by sirolimus has been reported [93-95] while Melzi et al found no significant adverse effect of sirolimus in islet engraftment [96]. Gao et al reported sirolimus and daclizumab did not show any individual or synergistic negative effects on islet proliferation [97]. However, insulin independence in Edmonton protocol was not sustained for a long-term resulting in 12.5% at 5 year after islet transplant [4].

2.3.3. Newer immunosuppression protocols

Recent clinical trials implementing monoclonal antibodies such as basiliximab (anti-IL-2 receptor)[70], efalizumab (anti-LFA-1)[89], alemtuzumab (anti-CD52)[83] have shown high rate of insulin independence after transplant. These monoclonal antibodies are produced as molecular targeting agents and considered as less likely to have direct effects on β cell function.

Currently major islet transplant centers are increasingly adopting stronger induction immunosuppression comprised of T cell depletion using anti-thymocyte globulin, alemtuzumab or OKT3 γ 1 (anti-CD3) plus anti-TNF- α treatment. This has resulted in significantly improved long-term maintenance of insulin independence [3, 5].

In maintenance immunosuppression, tacrolimus is still a key medication; although, there is controversy on the use of tacrolimus and its effect to islet graft function as described above (See § 2.5.1). Mycophenolate mofetil (MMF) is also used for maintenance immunosuppression, inhibiting proliferation of T and B cells and promoting apoptosis of activated T cells [98, 99]. Gallo et al recently showed that MMF was able to reduce survival of β cells, impair glucose-stimulated insulin secretion and β cell proliferation [100]. Posselt et al reported excellent islet transplant outcome using CNI-free immunosuppression that included belatacept [89], which is a fusion protein with Fc fragment of a human IgG linked to cytotoxic T lymphocyte-associated antigen 4 (CTLA-4) that allows costimulation blockade of CD80 and CD86 on antigen presenting cells [101]. Overall islet investigators have continued to make

efforts to find effective immunosuppression with less effect on β cell function while enhancing β cell function such as exenatide which is a glucagon-like peptide-1 (GLP-1) analog [75].

2.4. Islet encapsulation

The islet encapsulation aims to eliminate or reduce the dose of immunosuppression, which is a major obstacle in current islet transplantation, by isolating islets from blood flow and avoiding direct interaction with antibodies and immune cells such as lymphocytes and macrophages. However, few clinical trials using encapsulation technique have been reported [91, 102]. The University of Perugia group demonstrated the efficacy of microencapsulated human islets with sodium alginate in 4 type 1 diabetic patients, who were able to reduce HbA1c level and the amounts of exogenous insulin injection [91]. Elliot RB et al. showed a case report on xenotransplantation using alginate-encapsulated porcine islets, also allowing reduction of insulin dose [102]. In both reports, islet recipients did not use any immunosuppressants although insulin independence was not achieved, suggesting the advantage and limitation of current encapsulation strategy (Figure 1).

There are several methods of islet encapsulation; macrocapsular devices, microencapsulation and surface modification. A macrocapsular device that is composed of polytetrafluoroethylene membrane enabled delayed onset of diabetes in mice model [103]. Microencapsulation of islets has been prepared using various materials such as alginate, agarose and collagen [104-106]. An issue of microencapsulation is the enlargement of the size of islet mass; microencapsulation of an islet can increase the size by as much as 3 to 5 folds of the original islet. Alternatively, surface modification of islets is a strategy to reduce the tissue volume. Polyethylene glycol (PEG) is a hydrogen polymer and can be used for conformal coating to encapsulate islets in the process of polymerization [107]. PEGylation, i.e. PEG conjugation at the islet surface, is the another way of islet encapsulation without significant increase in tissue size [108]. Recently, PEGylation attached with biologically active agents of heparin, activated protein C, urokinase or thrombomodulin has been developed to prevent the local coagulation immediately after islet infusion [109-112]. These techniques were recently developed and the sustainability of PEGylation needs to be proven.

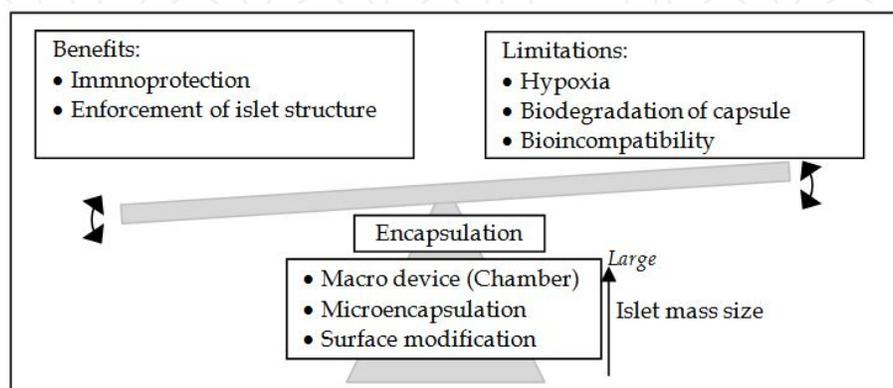


Figure 1. Benefits and current limitations of islet encapsulation.

3. Clinical assessment of beta cell function

Monitoring graft function is a major concern in clinical management of islet recipients since islet graft dysfunction in both acute phase after transplant and chronic phase is an obstacle to its widespread use as a standard care for type 1 diabetes. Furthermore, isolated islets are transplanted via the portal vein into the liver, making it difficult to employ biopsy examination of engrafted islets. Hence, several methodologies to predict islet graft function indirectly have been proposed. In this section, indices currently available for clinical assessment of islet graft function are discussed (Table 5).

3.1. Blood tests and clinical indices

3.1.1. Glucose tolerance/stimulation test

Glucose tolerance test (GTT) is a basic assessment method to diagnose diabetes although glucose stimulation; in itself has risk of artificial hyperglycemia for type 1 diabetic patients. Baidal et al reported that acute insulin/C-peptide release, mixed meal stimulation index, time-to-peak C-peptide, 90min glucose level and area under the curve of glucose values could predict islet dysfunction [113]. Arginine stimulation test is also useful for the evaluation of islet graft function. Glucose-potential slope and the maximal response in arginine stimulation test were significantly associated with β cell secretory capacity in a report from University of Pennsylvania group [114].

3.1.2. HYPO score and LI

Hypoglycemic (HYPO) score and lability index (LI) are calculated based on patients' journals of self-monitoring blood glucose (SMBG) for a month, providing a link to graft function through the quality of glycemic control [115]. These assessment tools are beneficial since a major endpoint of clinical allogeneic islet transplantation is to prevent hypoglycemic events; however, HYPO and LI calculations require a number of glucose measurements and hence are only calculated on a monthly or yearly basis using a complex scoring system.

3.1.3. SUIITO index

A simple evaluation method using fasting blood glucose and C-peptide levels has been proposed, called secretory unit of islet transplant objects (SUIITO) index [116]. The SUIITO index was originally developed using the concept of the homeostasis model assessment for insulin secretion (HOMA- β) model, where healthy person has 100 of SUIITO index. The calculation uses serum C-peptide levels instead of insulin levels, since islet recipient may be administering exogenous insulin during graft dysfunction and overlapped measurement of endogenous and exogenous insulin amounts are avoided [117]. SUIITO index can provide reference

value for insulin independence and elimination of hypoglycemia [118]. In addition, SUIITO index allows extensive link to quality of life in islet recipients [119].

*3.1.4. C-peptide/glucose ratio and C-peptide/glucose*creatinine ratio*

C-peptide per glucose ratio (CP/G) is also a simple technique to predict islet graft function using blood glucose and C-peptide, similar to the SUIITO index [120]. To correct islet graft function in patients with renal dysfunction, C-peptide/glucose*creatinine ratio has also been proposed. University of Miami group showed that CP/G correlated with 90min glucose level and β score [120].

3.1.5. β score

This scoring system uses data on fasting blood glucose, HbA1c, stimulated C-peptide, and absence of insulin or oral diabetic medication, that cover multiple aspect of glycemic control in islet recipients [121]. Correlation between β score and 90 min glucose level after mixed meal tolerance test has also been reported.

3.1.6. TEF

Transplant estimated function (TEF) is calculated by a formula using daily exogenous insulin requirements and HbA1c, that are routinely measured at clinic, eliminating glucose stimulation test when compared to β score [122]. TEF correlated well with β score and insulin response to arginine stimulation test.

3.1.7. TFIM model

Transplanted functional islet mass (TFIM) model is a recently proposed index that is aimed to guide the decision to use a specific islet preparation [123]. TFIM model is composed of transplanted islet volume, increment of insulin secretion, cold ischemia time and exocrine tissue volume transplanted, and can predict islet graft function.

3.2. Clinical image study

Functional mass of transplanted islets can be observed by the combination of the radioisotope-labeled grafts using 18F-fluorodeoxyglucose (^{18}F FDG) and positron emission tomography with computed tomography (PET/CT) [124, 125]. Although this technique is only applicable to capture early phase of transplantation up to 60 min after transplant, islet graft loss as well as transplanted islet distribution in the liver can be observed. Nano-iron particle also visualizes engrafted islet mass using magnetic resonance imaging (MRI) and allows longer follow-up when compared to PET/CT technique [126, 127].

Method	Variables required	Advantage	Disadvantage	Reference
GTT	A series of glucose or C-peptide values during glucose stimulation	Widely available method in clinic	The risk of hyperglycemia Repeated blood collection	[113, 114]
HYPO score and LI	Detailed self-recorded journal of glucose levels and hypoglycemic episodes	Direct evaluation of hypoglycemia that is a major outcome in islet transplantation	Number of records for monthly basis are required Complex calculation for LI	[115]
SUITO index	Fasting serum C-peptide and glucose level	Simple calculation Easy prediction of graft function corresponding to insulin independence.	Limited application to other species	[118, 119]
CP/G	Fasting serum C-peptide and glucose level	Simple calculation	Limited information on extended outcomes of hypoglycemia	[120]
β score	Fasting glucose, HbA1c, Daily insulin dose, Stimulated C-peptide	To capture multiple aspects of glycemic control	Composite scoring system requiring 4 variables including the results from glucose stimulation test	[121]
TEF	A series of records on HbA1c and daily insulin amounts	To eliminate glucose stimulation test compared to β score Calculation using variables that can be collected in standard diabetes care	Adjustment of coefficients by individual patient	[122, 128]
TFIM Model	Volume of transplanted islets, increment of insulin secretion, cold ischemia time and volume of transplanted exocrine tissue	To follow graft function using isolation results	Validated using data on islet after kidney transplantation	[123]
Radiologic imaging technique; PET/CT	Radioisotope-labeled islets PET/CT machine	To allow evaluation of islet graft mass and the distribution in the liver	The measurement only applicable for early phase of transplantation due to half-time of radioisotope Labeling procedure required	[124, 125]
Radiologic imaging technique; MRI	Iron-nanoparticle labeled islets MRI machine	To allow longitudinal follow up of islet mass	Labeling procedure required Iron overload	[126, 127]

Table 5. Clinical assessment of β cell function

3.3. Autologous Islet Transplantation

Patients with refractory chronic pancreatitis undergo total or partial pancreatectomy to alleviate pain and also autologous islet transplantation to retain pancreatic endocrine function after surgery. Islets isolated from pancreas are infused intraportally into the liver. Assessment of beta cell function in such autologous islet transplant patients typically follows the methods described for allogeneic islet transplantation. For example, the SUIITO index can be applicable to autologous islet transplantation and was founded as an excellent predictor of insulin independence [129]. However, no immune response against infused islets is expected in these patients. Post-transplant function of autologous islets has been shown to be much better than in allogeneic combination; β cell mass more than 10,000 IEQ/kg of islet yield is considered for a factor of insulin independence in allogeneic transplants while islet yield over 5,000 IEQ/kg is the successful factor in autologous transplantation [130]. After achievement of insulin independent status, patients receiving autologous islets have better long term survival of graft. Most patients also achieve significant relief from pain and improve their quality of life.

4. Conclusion

Islet transplantation has been shown to be a very promising treatment that could result in freedom from requirement of exogenous insulin in type 1 diabetic patients. One of the major advantages of islet transplantation is the minimally invasive nature of the procedure when compared to whole organ pancreas transplantation. Despite its wide spread use at several major transplant centers, the volume of patients receiving islet transplants remain low when compared to the number of "brittle" type 1 diabetic patients eligible for this procedure. Recently impressive gains have been made in the improvement of post-transplant islet function. This is primarily due to the use of T-cell depleting immunosuppression during induction phase after transplant followed by use of tacrolimus, rapamycin and or mycophenolic mofetil during the maintenance phase. In addition several advances made in donor selection, pancreas procurement, enzymatic digestion, islet purification and islet culture seem to have contributed to this success. Recent completion of a large scale phase III clinical trial sponsored by the NIH has given hope that soon this procedure may be approved for clinical use. In light of these advances, there is optimism that the remaining hurdles could be overcome to improve the long term function of the transplanted islets.

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