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Clinical Allogeneic and Autologous Islet Cell Transplantation: Update

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Islet cell transplantation is categorized as a β-cell replacement therapy for diabetic patients who lack the ability to secrete insulin. Allogeneic islet cell transplantation is for the treatment of type 1 diabetes, and autologous islet cell transplantation is for the prevention of surgical diabetes after a total pancreatectomy. The issues of allogeneic islet cell transplantation include poor efficacy of islet isolation, the need for multiple donor pancreata, difficulty maintaining insulin independence and undesirable side effects of immunosuppressive drugs. Those issues have been solved step by step and allogeneic islet cell transplantation is almost ready to be the standard therapy. The donor shortage will be the next issue and marginal and/or living donor islet cell transplantation might alleviate the issue. Xeno-islet cell transplantation, β-cell regeneration from human stem cells and gene induction of the naïve pancreas represent the next generation of β-cell replacement therapy. Autologous islet cell transplantation after total pancreatectomy for the treatment of chronic pancreatitis with severe abdominal pain is the standard therapy, even though only limited centers are able to perform this treatment. Remote center autologous islet cell transplantation is an attractive option for hospitals performing total pancreatectomies without the proper islet isolation facilities.

Keywords: Allogeneic islet cell transplantation; Autologous islet cell transplantation; Diabetes mellitus, type 1; Pancreatitis, chronic; SUITO index

INTRODUCTION

Islet cell transplantation is categorized as a β-cell replacement therapy for diabetic patients who lack the ability to secrete insulin [1]. Islets possess their own glucose sensor, produce insulin, release insulin in response to glucose, maintain normoglycemia, and function indefinitely [1]. Therefore, β-cell replacement by islet cell transplantation can reverse or prevent diabetes.

The two types of clinical islet cell transplants that have been performed include allogeneic islet cell transplantation for the treatment of type 1 diabetes and autologous islet cell transplantation for the prevention of surgical diabetes after a total pancreatectomy.

Allogeneic islet cell transplantation has several hurdles such as unstable outcomes of islet isolation, the need for multiple donor pancreata and transplants, difficulty maintaining insulin independence, and detrimental side effects from immunosuppressants to be overcome before becoming a standard therapy [1]. After the publication of the Edmonton protocol [2], clinical allogeneic islet cell transplantation has been substantially improved over the past decade [3].

On the other hand, autologous islet cell transplantation after total pancreatectomy for the treatment of chronic pancreatitis with intractable abdominal pain has become the standard therapy [4]. This treatment efficiently reduces abdominal pain by total pancreatectomy while avoiding brittle diabetes by autologous islet cell transplantation.

In this review article, current status and advances of both allogeneic and autologous islet cell transplantation are described.

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ALLOGENEIC ISLET CELL TRANSPLANTATION FOR THE TREATMENT OF TYPE 1 DIABETES

In 2000, the University of Alberta group published that 7 out of 7 type 1 diabetic patients became insulin independent after allogeneic islet cell transplantation [2]. The protocol of this publication was called the Edmonton protocol and this procedure was sensational because a minimally invasive cell therapy was able to reverse diabetes. After the publication of the Edmonton protocol, the number of clinical allogeneic islet cell transplantation has increased [3]. When the Edmonton protocol was attempted, some islet transplantation centers were able to duplicate the outcomes [5] but other centers were not able to achieve similar success [6]. In order to confirm the results of the Edmonton protocol, a multi-center, international clinical trial was conducted [7]. This international, multi-center clinical trial revealed that achieving insulin independence after allogenic islet cell transplantation depended on a team of personnel possessing previous experience with islet isolation and islet cell transplantation. Islet isolation outcomes were not stable even at the advanced islet transplantation centers. The Edmonton protocol required two or more islet transplants because; the islet isolation process yielded unstable outcomes leading to inefficient islet transplantation. Actually the study found that success rate of islet isolation was 30% to 50%, therefore 4 to 6 donor pancreata were necessary to achieve insulin independence for one type 1 diabetic patient. Thus, poor efficacy became one of the major issues of islet cell transplantation.

In 2005, long-term clinical outcomes of the Edmonton protocol were published from the University of Alberta group [8]. This report demonstrated that approximately 80% of patients maintained viable transplanted islets; however, only less than 10% of patients could maintain insulin independence 5 years after islet cell transplantation. The issue of maintaining insulin independence became another major challenge for clinical islet cell transplantation.

Even though the Edmonton protocol avoids glucocorticoid steroid [2], other immunosuppressive drugs have side effects. One notable example is the combination of sirolimus and tacrolimus, which damages renal function [9]. In addition, others and we have found that an islet cell transplantation recipient experiences an average of more than one serious adverse event (life-threatening or death) [3,10]. Deleterious side effects of immunosuppression are an additional issue of islet cell transplantation.

During this decade these issues have been widely addressed and significant improvements have been achieved.

ISSUES AND POTENTIAL SOLUTIONS FOR ALLOGENEIC ISLET CELL TRANSPLANTATION

Variable outcome of islet isolation

Even at the advanced islet transplantation centers, the outcome of human islet isolation varies [11,12]. The success of human islet isolation depends upon the quality of the donor, the pancreas preservation, the efficacy of pancreas digestion and islet purification. In order to increase the success rate of human islet isolations, each step needs to be improved.

Pancreas donor criteria for successful islet isolation have been explored [13-16]. High body mass index, lack of fibrosis, and normal blood chemistry have shown to be the important factors for successful islet isolation.

In terms of pancreas preservation, the two-layer pancreas preservation method has proven to be better than simple storage with the University of Wisconsin solution [17-22]. However, the two-layer preservation method requires expertise when it is applied to human pancreas preservation [23-25]. Furthermore, the pancreatic duct also requires adequate preservation, because the pancreatic duct is used to perfuse collagenase for islet isolation. Pancreatic ductal injection was shown to protect the pancreatic duct effectively and improve the outcome of islet isolation [26-28].

During the digestion step, over-digestion of isolated islets needs to be avoided. Trypsin inhibition could prevent over-digestion [21,29]. However, the importance of trypsin inhibition is contentious when the donor pancreas is intact [30].

Islet cells are purified by exploiting the density difference between islet cells and exocrine tissue. This density gradient is established by the COBE 2991 cell processor [1,2]. To generate the density gradient, Ficoll is generally used; however, Ficoll is not an ideal material due to its high viscosity and possible endotoxin contamination [31,32]. Iodixanol, which was originally developed for X-ray contrast, has been shown to be a better material for the density gradient solution [32-37].

With the combination of the two-layer pancreas preservation, the pancreatic ductal injection by surgeons who belongs to islet isolation team and the iodixanol based density gradient, our success rate of human islet isolation is approximately 90%

[38]. Hence unstable outcomes of islet isolation can be solved with current advanced methods.

Necessity of multiple transplants to achieve insulin independence

One of the drawbacks of the Edmonton protocol is the necessity of multiple donor pancreata and islet cell transplants to achieve insulin independence. However, the University of Minnesota group demonstrated that single donor islet cell transplantation to achieve insulin independence was possible using anti-inflammatory drugs combined with immunosuppression induction therapy using thymoglobulin [39]. We also reported successful single donor islet cell transplantation cases using an improved islet isolation method and potent anti-inflammatory drugs combined with immunosuppression induction therapy using thymoglobulin [40,41]. Posselt et al. [42] demonstrated that 50% (4/8) of patients achieved insulin independence after single donor islet cell transplantation with immunosuppression induction therapy using thymoglobulin combined with the anti-LFA-1 antibody 'efalizumab.' Recently, the University of Alberta group demonstrated that insulin and heparin infusions during the peri-transplant period improved the success rate of single donor islet cell transplantation [43]. Taking these facts together, improved engraftments of transplanted islets in the early phase of transplantation should be the key for successful single donor islet cell transplantation. Immunosuppression induction therapy using thymoglobulin, anti-inflammation therapy and supplements of insulin and heparin were important strategies. In addition, the transplantation of many high quality islets should be the other important factor [40,41].

Issues with maintaining insulin independence

Poor long-term insulin independence was a great disappointment of the Edmonton protocol. Our recent survey of opinions from type 1 diabetic patients demonstrated that more than 80% of patients wished to become insulin independent [44]. Becoming insulin independent is a strong motivating factor for accepting islet cell transplantation.

The University of Minnesota group demonstrated that 4 out of 6 patients maintained insulin independence at a mean of 3.4 years after islet cell transplantation by immunosuppression induction using thymoglobulin combined with anti-TNF alpha antibody treatment [45]. They transplanted an average of more than 11,000 islet equivalent (IEQ)/kg body weight using two pancreata for three cases and one pancreas for one case. Transplantation of a high number of islet cells seems to be another important factor. The University of Miami group demonstrated that supplemental islet cell infusion with the GLP-1 analog 'exenatide' and the anti-TNF alpha antibody 'etanercept' enabled them to achieve long-term insulin independence [46]. Under this protocol, four out of four patients achieved the long-term insulin independence (18 months). The average islet yield per body weight for the supplemental islet cell infusion was 5,613 IEQ/kg. Hence, adding a supplemental islet cell infusion after an initially successful islet graft function fails should be an excellent strategy for achieving long-term insulin independence.

In both the University of Minnesota and the University of Miami strategies, multiple islet cell transplants were necessary to maintain long-term insulin independence. Therefore, the timing of the additional islet cell transplants is important to maintain insulin independence. We demonstrated that maintaining enough functional islet graft mass was associated with insulin independence [47]. We developed a new index (secretory unit of islet transplant objects, SUITO index) which could reflect functional islet mass. The formula of the SUITO index is as follows: fasting C-peptide [ng/mL]/(fasting glucose [mg/dL]-63)×1,500 [48,49]. A SUITO index of more than 26 was associated insulin independence. Therefore we postulated that when the SUITO index decreased and became close to 26, it was the appropriate time for a supplemental islet cell infusion. We experienced a unique case of prolonged insulin independence (more than 2 years) in which a patient received total more than 20,000 IEQ/kg body weight after two islet cell transplants [49]. Her SUITO index remained higher than 30 for more than two years under the Edmonton type immunosuppression without thymoglobulin induction. This case suggests that when a high quantity of islet cells is transplanted, prolonged insulin independence is achievable without the need for immunosuppression induction therapy using thymoglobulin. Recently we experienced prolonged insulin independence after single donor islet cell transplantation [40,41]. The patient has been insulin independent for more than 18 months after single islet cell transplantation. In this case, we used thymoglobulin induction with potent anti-inflammatory drugs, and the transplanted islet yield was 12,200 IEQ/kg body weight [40,41]. This case suggests that it is possible to achieve prolonged insulin independence with a single donor islet cell transplantation combined with immunosuppression induction using thymoglobulin and anti-inflammatory drug administration.

Side effects of immunosuppressants

The side effects of immunosuppressants are a common problem among all allogeneic transplantations. The Edmonton protocol has unique problems related to the high dose of sirolimus [2,10,42]. High concentrations of sirolimus cause painful oral ulcers, peripheral edema, poor wound healing and thinning nails. Those side effects are not life-threatening however; the quality of life deteriorates for transplant patients. In addition, the combination of tacrolimus and sirolimus causes proteinuria and deterioration of renal function [9]. Since one of the expected results of islet transplantation is to prevent secondary diabetic complication including diabetic nephropathy, the side effect of poor kidney function is unacceptable.

In order to minimize the side effects of immunosuppressants, we eliminated sirolimus from our immunosuppression therapy after islet transplantation [40,41]. This protocol has dramatically reduced the side effects of immunosuppressants.

FUTURE DIRECTION OF β-CELL REPLACEMENT THERAPY FOR TYPE 1 DIABETES

As mentioned above, all current major drawbacks of islet cell transplantation should be solved in near future. Then, islet cell transplantation for the treatment of type 1 diabetes will become the standard therapy. Donor shortage is the next issue to be solved. Marginal donor islet cell transplantation and living donor islet cell transplantation could alleviate the donor shortage. Since the number of cadaveric donors for islet cell transplantation was extremely low in Japan [50], both islet transplants using marginal donors [34] and a living donor [51,52] were performed in Japan. Therefore, these options could be implemented with the current islet cell transplantation protocol.

Xeno-islet cell transplantation using pig islets could solve the issue of donor shortage. Encapsulated porcine islets [53] and porcine islet containing devices [54] were transplanted into type 1 diabetic patients. The efficiencies of both clinical transplants were less compared to allogeneic islet cell transplantation. Further improvements are necessary to expand the efficacy of xeno-islet cell transplantation.

β-cell regeneration using human stem cells has the potential to treat diabetes. The efficacy of β-cell regeneration and the safety of generated cells are major issues for their clinical application. Kroon et al. [55] demonstrated that pancreatic endoderm derived from human embryonic stem cells generated glucose-responsive insulin-secreting cells *in vivo*. However, none of generated β-cells from human stem cells ever reversed diabetes in mice. Therefore, improved efficacy is the important next step for β-cell generation using stem cells.

Gene delivery directly to a patient's pancreas for β-cell regeneration is an attractive treatment, since no transplantation is necessary. Recently, we demonstrated that gene delivery using micro-bubble destruction technology successfully delivered NeuroD into the pancreas of diabetic rats and reversed diabetes [56]. Further studies including a large animal model are necessary to confirm the safety and efficacy; however, this shows potential to be the next generation of diabetes treatment.

AUTOLOGOUS ISLET CELL TRANSPLANTATION TO PREVENT SURGICAL DIABETES

Autologous islet cell transplantation after a total or semi-total pancreatectomy for chronic pancreatitis with severe abdominal pain is an established treatment [4]. Total pancreatectomy effectively reduces abdominal pains even for patients requiring narcotics for the abdominal pains [4,57,58]. While transplantation of autologous islet cells isolated from a pancreas with choric pancreatitis can prevent surgical diabetes [4,57,58]. Autologous islet transplants were also applied to total pancreatectomies of benign pancreatic tumors [59] and pancreatic trauma [60].

The clinical outcome for metabolic control is excellent after autologous islet cell transplantation compared to allogeneic islet cell transplantation. The differences between the two transplantation therapies are shown in Table 1. The reasons for the favor-

Table 1. Differences between allogeneic islet transplantation and autologous islet transplantation

Characteristic	Allogeneic	Autologous
Diseases	Type 1 diabetes	Surgical diabetes
Auto-immunogenicity	Yes	No
Allo-immunogenicity	Yes	No
Necessity of anti-rejection drugs	Yes	No
Pancreas suffered cytokine storms	Yes	No
Cold ischemic period	Variable	Short
Storage period after islet isolation	Variable	Short
Islet progenitor cells	Less	More

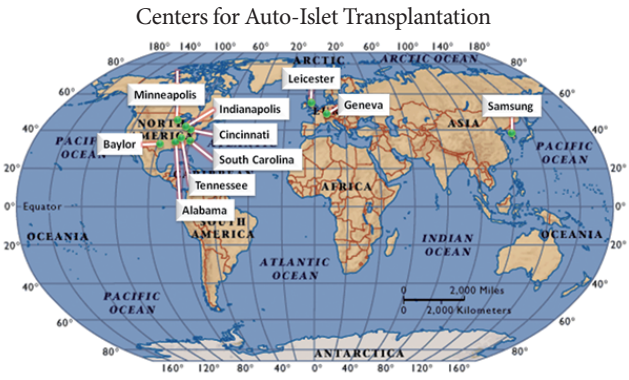

Fig. 1. Centers for autologous islet cell transplantation in the world. Currently only limited centers perform the autologous islet cell transplantation to prevent surgical diabetes.

able results of autologous islet cell transplantation are thought to be 1) patients have no auto-immune disease, 2) transplanted islets do not suffer allogeneic rejection, 3) diabetogenic anti-rejection drugs are not required, 4) pancreata do not suffer cytokine storms during brain-dead periods, 5) the cold preservation period for retrieved pancreata is short, 6) isolated islets are immediately transplanted without culture, and 7) pancreata from chronic pancreatitis might have more islet progenitor cells in their pancreatic ducts [61].

Even though autologous islet cell transplantation after total pancreatectomy is an established therapy for chronic pancreatitis with severe abdominal pain, only a limited number of centers perform this therapy (Fig. 1). The requirements of current good manufacturing practice (cGMP) facilities for the clinical islet isolation procedure limit the availability of this therapy. The cGMP facility is especially expensive due to its maintenance requirements, therefore only limited hospitals have such facilities. Recently, successful remote center autologous islet cell transplantation was reported [60]. In this case, the pancreas was surgically removed for the treatment of pancreatic trauma and was shipped to the islet isolation center, and then isolated islets were sent back to the hospital. In the case of total pancreatectomy for chronic pancreatitis, the removed pancreas should be sent to an islet isolation center for autologous islet cell transplantation if the hospital does not have islet isolation facility.

CONCLUSION

Allogeneic islet cell transplantation has dramatically improved and is ready to be the standard therapy for the treatment of type 1 diabetes. Donor shortage is the next issue and can be addressed by marginal and/or living donor islet cell transplantation, xeno islet cell transplantation and β-cell regeneration.

Autologous islet cell transplantation is an effective treatment for chronic pancreatitis with severe abdominal pain. Remote center autologous islet cell transplantation should be considered when a total pancreatectomy is performed in a hospital not possessing an islet isolation center.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

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