World Journal of Transplantation

Online Submissions: http://www.wjgnet.com/esps/
bpgoffice@wjgnet.com
doi:10.5500/wjt.v3.i4.48

World J Transplant 2013 December 24; 3(4): 48-53
ISSN 2220-3230 (online)

EDITORIAL

Current status of clinical islet transplantation

Andrew R Pepper, Boris Gala-Lopez, Oliver Ziff, AM James Shapiro

Andrew R Pepper, Boris Gala-Lopez, AM James Shapiro, Department of Clinical Islet Transplant Program, University of Alberta, Edmonton T6G 2C8, Alberta, Canada
Oliver Ziff, AM James Shapiro, Department of Surgery, University of Alberta, Edmonton T6G 2B7, Alberta, Canada
Author contributions: Pepper AR and Gala-Lopez B contributed equally to this work designing the research and writing the paper; Ziff O performed bibliographic revision and designed figures; Shapiro AMJ designed the research and revised the final manuscript as senior author.
Correspondence to: AM James Shapiro, MD, PhD, Professor, Director of Clinical Islet and Living Donor Liver Transplant Programs, Department of Clinical Islet Transplant Program, University of Alberta, 2000 College Plaza, 8215-112th St, Edmonton T6G 2C8, Alberta, Canada. amjs@islet.ca
Telephone: +1-780-4077330 Fax: +1-780-4078259
Received: July 26, 2013 Revised: August 16, 2013
Accepted: August 28, 2013
Published online: December 24, 2013

Abstract

Islet transplantation (IT) is today a well-established treatment modality for selected patients with type 1 diabetes mellitus (T1DM). After the success of the University of Alberta group with a modified approach to the immune protection of islets, the international experience grew along with the numbers of transplants in highly specialized centers. Yet, long-term analysis of those initial results from the Edmonton group indicated that insulin-independence was not durable and most patients return to modest amounts of insulin around the fifth year, without recurrent hypoglycemia events. Many phenomena have been identified as limiting factor for the islet engraftment and survival, and today all efforts are aimed to improve the quality of islets and their engrafting process, as well as more optimized immunosuppression to facilitate tolerance and ultimately, better long term survival. This brief overview presents recent progress in IT. A concise historical perspective is provided, along with the latest efforts to improve islet engraftment, immune protection and ultimately, prolonged graft survival. It is apparent that as the community continues to work together further optimizing IT, it is hopeful a cure for T1DM will soon be achievable.

Key words: Islet transplantation; Type 1 diabetes; Immunosuppression

Core tip: Since the initial inception of the "Edmonton protocol", phenomenal progress has transpired in the last decade. These milestones were namely due to the implementation of numerous pre-clinical and clinical investigations, testing innovative agents allowing potent immunotolerance with minimal complications as well as alternative transplant sites to overcome limitations inherent to the current intraportal access. As a result nearly 80% of full or partial graft function, out of more than 300 transplants performed to date. As the field of continues to work and progress together, it is foreseeable that a cure for type 1 diabetes mellitus is obtainable in the near future.

Pepper AR, Gala-Lopez B, Ziff O, Shapiro AMJ. Current status of clinical islet transplantation. *World J Transplant* 2013; 3(4): 48-53 Available from: URL: http://www.wjgnet.com/2220-3230/full/v3/i4/48.htm DOI: http://dx.doi.org/10.5500/wjt.v3.i4.48

INTRODUCTION

Islet transplantation (IT) is today an accepted modality to treat selected diabetic patients with frequent hypoglycemics and severe glycemic lability[1,2]. The "Edmonton Protocol" became a milestone by reporting sustained C-peptide production and high rates of insulin-independence after transplant in type 1 diabetes mellitus (T1DM)[3]. This reality became possible with the use of newer, more potent immunosuppressant (IS) agents, the avoidance of corticosteroids, and high-quality islet preparations, al-

though typically two islet infusions were required to attain insulin independence.

Long-term analysis of these initial results from the Edmonton group indicated that insulin-independence was not durable and most patients return to moderate amounts of insulin approximately 5 years post-infusion, in the absences of recurrent hypoglycemia events[4,5].

Causes for this chronic graft function remain unclear, but are likely associated with immune rejection, recurrence of autoimmunity or chronic exposure to diabetogenic IS agents[5,6].

This brief overview presents recent progress in IT. A succinct historical viewpoint is provided, along with the resent efforts to improve islet engraftment, immune protection and ultimately, prolonged graft survival.

HISTORICAL PERSPECTIVE

The history of IT is filled with numerous sacrifices and hardly fought successes. Early rudimentary experiments in the 19th Century lead to the concept of isolation and purification[5]. In 1966, the University of Minnesota group performed the first clinical attempt to cure T1DM by whole pancreas transplant[7,8]. It allowed technical improvements, but more importantly, refinements in IS while introducing cyclosporine continued with the use of multiple and more potent drug schemes.

Clinical investigators at Washington University demonstrated the possibility of reversing diabetes with temporary insulin independence after transplantation of human islets. It was a transient success because IS was still insufficient[9]. A year later, the first successful series of human islet allografts was reported by the University of Pittsburgh, achieving prolonged insulin-independence with a more optimized IS based on the recently introduced agent FK-506 and no steroids[9].

Another important milestone was the report from the University of Alberta group showing successful long-term results on selected patients, with the use of a novel IS scheme. Grafts were non-human leukocyte antigen (HLA) matched, patients were not sensitized (negative panel reactive antibody pre-transplant), islets were ABO compatible, and sequential transplants were used to deliver an adequate islet infusion mass by a percutaneous portal venous access route. Immunosuppression was tailored to avoid steroids and minimize calcineurin inhibitors to prevent diabetogenicity, with the combination of sirolimus, low-dose tacrolimus (TAC), and the daclizumab induction[10].

New programs proliferated worldwide based on the lessons learned from the "Edmonton Protocol" and the number of transplant significantly increased over the coming years. However, insulin independence was not durable long-term and most patient returned to modest amounts of insulin without risk of recurrent hypoglycemia by the third to fifth year. Additionally, approximately 25% required additional late islet infusions during the second or third year post-transplant[2].

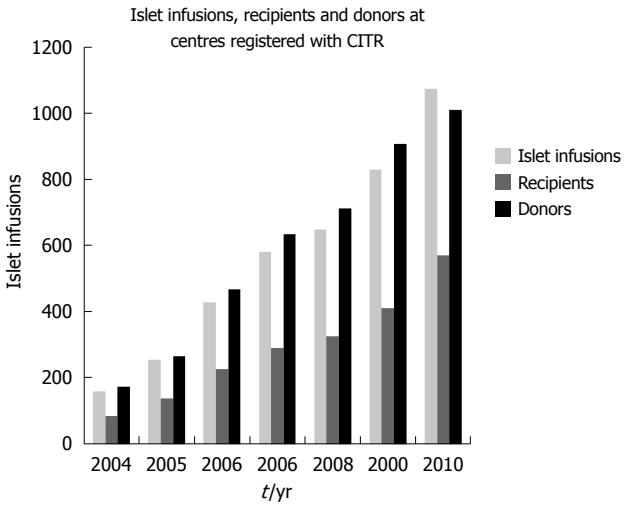

Figure 1 Total number of recent islet allograft infusion per recipient per donor in CITR-participating centers (2004-2010). Data adapted from 2010 CITR Seventh Annual Report.

New efforts are now aimed to improve the quality of islets, enhanced their engraftment conditions and prolonged their function. Moreover, new transplant sites are also consider overcoming the limitations of the traditional intraportal site and providing a suitable framework for future strategies, such as the use of insulin-producing stem cells as surrogate for the precious and increasingly scarce human islets.

EDMONTON'S CURRENT RESULTS

Despite significant improvements in the care of T1DM patients, a subgroup remains in significant disadvantage due to refractory hypoglycemia. The option of IT offers the possibility of improved glycemic control[2]. The recent years have witnessed substantial progress in the number and results of IT (Figure 1).

Before the year 2000, few centers performing IT achieved high rates of sustainable insulin independence after this procedure[2]. In 2000, Shapiro *et al*[3] reported their initial findings in seven consecutive subjects treated with glucocorticoid-free immunosuppressive therapy combined with infusion of an adequate mass of freshly prepared, bringing a new perspective on the immunoprotection provided for these patients[3]. The success achieved with this new scheme prompted interest and enthusiasm among various programs and launched a major international trial with key results for our current concepts on immunosuppression.

Today, the Clinical Islet Transplant Program at the University of Alberta remains as one of the most important and active transplant center in the world after becoming a beacon with one of the most integral and successful approaches to IT with sustained and reproducible long-term results. The task remains improving the viability of islet preparations and also in determining the most optimal IS agents to improve the initial results published

Table 1 Summary of current open clinical trials with interventions in islet transplantation (Adapted from Clinical Trials.gov)

Trial ID	Description	Institution
NCT01653899	Caspase Inhibition in Islet Transplantation	University of Alberta
NCT00468117	Efficacy of Islet After Kidney Transplantation	National Institute of Allergy and Infectious Diseases
NCT01705899	Islet Allotransplantation in Type 1 Diabetes	Ohio State University
NCT01652911	A Phase Ⅰ / Ⅱ Study of the Safety and Efficacy of Sernova's Cell Pouch™ for Therapeutic Islet Transplantation	University of Alberta
NCT00784966	Islet After Kidney Transplant for Type 1 Diabetes	Virginia Commonwealth University
NCT00790257	Safety and Efficacy Study of Encapsulated Human Islets Allotransplantation to Treat Type 1 Diabetes	Cliniques universitaires Saint-Luc-Université Catholique de Louvain
NCT00853944	Effect of Sitagliptin on Graft Function Following Islet Transplantation	University of British Columbia
NCT00249652	Transplant and Addiction Project 1	National Institute on Drug Abuse
NCT00530686	Pancreatic Islet Cell Transplantation - A Novel Approach to Improve Islet Quality and Engraftment	Baylor Research Institute
NCT01123187	Islet Cell Transplantation in Patients With Type 1 Diabetes With Previous Kidney Transplantation	University Hospital, Lille
NCT01817959	Study to Assess Efficacy and Safety of Reparixin in Pancreatic Islet Transplantation	Dompé s.p.a.
NCT00679042	Islet Transplantation in Type 1 Diabetic Patients Using the University of Illinois at Chicago Protocol	University of Illinois
NCT00453817	Islet of Langerhans Graft Monitoring by Magnetic Resonance Imaging	University Hospital, Geneva
NCT00853424	A Comparison of Islet Cell Transplantation With Medical Therapy for the Treatment of Diabetic Eye Disease	University of British Columbia
NCT00789308	Safety and Effectiveness of Low Molecular Weight Sulfated Dextran in Islet Transplantation	National Institute of Allergy and Infectious Diseases
NCT01148680	Trial Comparing Metabolic Efficiency of Islet Graft to Intensive Insulin Therapy for Type 1 Diabetes's Treatment	University Hospital, Grenoble
NCT01241864	Islet Transplantation in Type 1 Diabetic Kidney Allograft	University of Chicago
NCT01722682	Bone Marrow vs Liver as Site for Islet Transplantation	Ospedale San Raffaele
NCT01630850	Islet Transplantation in Patients With\Brittle\"Type 1 Diabetes"	University of Chicago
NCT01186562	Sitagliptin Therapy to Improve Outcomes After Islet Autotransplant	University of Minnesota
NCT01285934	A Trial of High Dose Immunosuppression and Autologous Hematopoietic Stem Cell Support Versus Intensive Insulin Therapy in Adults With Early Onset T1DM	University of Sao Paulo General Hospital
NCT00646724	Cotransplantation of Islet and Mesenchymal Stem Cell in Type 1 Diabetic Patients	Fuzhou General Hospital
NCT01379729	Bet Cell Therapy in Diabetes Type 1	AZ-VUB
NCT01341899	Efficacy and Safety Study of Autologous Hematopoietic Stem Cell Transplantation to Treat New Onset Type 1 Diabetes	The Affiliated Nanjing Drum Tower Hospital of Nanjing University Medical School
NCT01736228	Open-label Investigation of the Safety and Efficacy of DIABECELL in Patients With T1DM	Living Cell Technologies
NCT01346098	Islet Autotransplantation in Patients at Very High-risk Pancreatic Anastomosis	Ospedale San Raffaele
NCT00989547	Cord Blood Infusion for T1DM	Technische Universität München
NCT00807651	Autologous Hematopoietic Stem Cell Transplantation for Early Onset Type 1 Diabetes	Shanghai Jiao Tong University School of Medicine
NCT01042301	Profiling of Original Cellular and Humoral Biomarkers of Type 1 Diabetes	Nantes University Hospital
NCT01350219	Stem Cell Educator Therapy in Type 1 Diabetes	Tianhe Stem Cell Biotechnologies Inc.
NCT00014911	Immunosuppressive Medications for Participants in ITN005CT	National Institute of Allergy and Infectious Diseases

with the "Edmonton Protocol", but also to achieve single donor insulin-independence, safety and tolerability.

A recent study published a cross-sectional analysis of the current Edmonton results. It showed 79% of full or partial graft function out of more than 300 transplants performed. The median duration of insulin independence was 34.6 and 11.0 mo for subjects with full or partial graft function, whereas the duration of C-peptide was 53.3 and 70.4 mo for those same patients[11].

Phenomenal progress has occurred in the last years due to the implementation of numerous findings from preclinical and clinical investigations testing different agents to allow better immunotolerance with lesser complications, novel devices to provide islets with a safer environment, as well as new transplant sites to overcome limitations inherent to the current intraportal access (Table 1).

MAIN CHALLENGES TO IT

It is apparent that in light of the therapeutic advantages of β-cell replacement through IT, numerous contributing factors hinder islet graft survival and function. These obstacles must be overcome in order for this therapy to become the ubiquitous alternative to pancreas transplantation and exogenous insulin administration. Despite intrahepatic islet infusion being the route of choice for over three decades[12,13] in both experimental and clinical settings, several complications with this approach exist which may account for islet graft attrition[14-18]. The liver indeed has an advantage of a multiple vascular supply, however, its parenchymal oxygen tension, is well below that of the pancreas and is not conducive to islet survival[19,20]. Furthermore, the infusion of islets into the liver

is associated with inherit procedural risks including but not limited to catheter-induced hemorrhage and thrombosis[21]. Disadvantages of this route of islet administration also include limited ability to image islet grafts post-transplant, incapacity to retrieve the graft if required, and restricted quantity of β-cell mass that can recipient can receive due to portal pressure elevation[14-18,21,22]. The innate immune system further contributes to a reduction in β cells mass acutely post-infusion into the patient's portal circulation. It is estimated that greater than 50% of the transplanted islets are lost within hours post infusion which is thought in part to be due to the immediate blood mediated inflammatory reaction and complement coagulation cascade, as evidenced by acute C-peptide release, and from quantitative positron emission tomography scan imagery[14-16,23-27]. These factors in conjunction with the diabetogenic action of the immunosuppressive drugs [*i.e.*, calcineurin inhibits, sirolimus, mycophenolate mofetil (MMF)][28], suboptimal islet revascularization[29,30], both the adaptive and innate immune responses, potential HLA-antigen[31-34] sensitization and lack of an effective means of determining islet potency prior to transplant, together contribute to an inept utilization of the small number of available cadaveric donor pancreata[16,17]. The difficulties and limitations associated with hepatic portal vein infusion have stimulated robust efforts into investigation strategies to improve islet engraftment, such as refined IS protocols, surrogate sources of β-cells (*i.e.*, stem cells or porcine islets) and alternative transplantation sites, in effort to increase the potential for long-term islet graft survival and function[16,18].

IMPROVING ISLET GRAFT FUNCTION

The early results from IT should be taken into context and compared to alternative treatments modalities. In contrast to pancreas transplantation, IT is still in its infancy. Roughly 750 type 1 diabetic patients have received an IT among the some 30 active international islet centers over the past decade. In comparison, approximately 30000 pancreas transplants have been conducted over the past three decades[35-38]. Despite the relatively low number of islet recipients, encouraging results with IT have recently been reported, such as the greater than 50% insulin-independent rates from solitary pancreas transplantation 5 years post-transplant has now been matched by IT in at least four independent centers, namely Edmonton, Minneapolis, Genva and Lille. It is evident that recent significant advances in islet preparation and immunosuppressive therapy have improved the efficacy and safety of IT to the point that it now challenges whole organ pancreas transplantation.

Due to the multiple pathways known to be involved in β-cell attrition, including the autoreactive and alloreactive immune response, as well as the alloresponse it can be argued that a monotherapy IS approach is improbable to further enhance IT outcomes. Indeed, strategies towards single-donor IT has begun by implementing multiple pathways blockades to IS cocktails, which face the challenges of promoting islet graft survival. Combining anti-inflammatory biologics to maintenance IS have led to improved single-donor success rates at the University of Minnesota[39,40]. The success rate of islet donor islet recipients has dramatically increased from 10%-40% when peritransplant insulin and heparin intervention has been employed[27]. Tumor necrosis factor-α blockage by etanercept has improved single-donor islet transplant outcomes as well[27,40-44]. In preclinical settings specific anti-inflammatory agents such as the interleukin-1 receptor antagonist anakinra and etanercept significantly increased marginal mass islet engraftment[41-45]. Furthermore, anti-apoptosis and growth stimulation [*i.e.*, glucagon-like peptide 1 (GLP-1)] have further demonstrated advantageous results in both preclinical and clinical studies, for instance the short acting GLP-1 analogue exenatide demonstrated an increased single-donor islet engraftment success rate[46-48]. Clonal depletion of alloreactive T cells appears promote a hyporesponsive environment and peripheral mechanisms of anergy, thus driving the shift towards tolerance[49,50]. The use of T-cell depletion induction methods such as alemtuzumab in conjunction with TAC/MMF have resulted in substantial improvements in long-term insulin-independence (> 5 years)[51,52]. In addition, a current example of the extraordinary progress that has been made when combine IS strategies are implemented, is the remarkable success that has been achieved when co-stimulation blockage using belatacept (inhibiting CD80-CD86 interactions) in conjunction with T-cell depletion induction and in the absence of calcineurin inhibitors led to insulin independence with islets from a single donor and prolonged allograft survival[6,53]. It is clear current immunosuppressive therapies have become well tolerated and safer for the recipient by minimizing the adverse side effects while improving islet engraftment.

CONCLUSION

Since the first pioneering experimental and clinical studies, substantial improvements have been made in IT, leading to the development of the "Edmonton Protocol". Over the past decade, since this protocols inception, continued progress in the field has resulted in markedly higher rates of single-islet recipient success rates as well as sustained insulin-independences (> 5 years). Not to be forgotten are the benefits for microvascular complications (*i.e.*, reduced retinopathy) and the amelioration of hypoglycemic unaware events following IT, in most cases irrespective of glycemic control. Despite the favourable long-term safety profile associated with IT, many unanswered questions still exist; namely, the causality of islet graft function and attrition. For instance reduction in HbA1C and hypoglycaemia normally attributed to graft function may in part be a reflection of close glycemic monitoring. Equally, graft dysfunction and poor glycemic control post-transplant may be attributed to poor adher-

ence and psychosocial influences among others, rather than exclusively caused by islet graft loss[54]. Some of these answers may very well indeed be answered through randomized clinical trials. By no means should IT be perceived as a cure for all type 1 diabetics, however for a subset of individuals with severe glycemic lability, IT has been demonstrated to be an excellent therapeutic strategy to achieve glycemic control and abrogation of hypoglycaemia. As the field of continues to work and progress together, in effort to refine and optimized IT, it is foreseeable that a cure for T1DM is obtainable in the not so distant future.

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