IHE Report

Islet Transplantation for the Treatment of Type 1 Diabetes – An Update

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ISLET TRANSPLANTATION FOR THE TREATMENT OF TYPE 1 DIABETES – AN UPDATE

Prepared by:

Bing Guo
Paula Corabian
Christa Harstall

EXECUTIVE SUMMARY

Background

Type 1 diabetes, previously known as insulin-dependent or juvenile onset diabetes, is primarily a result of progressive destruction of the insulin secreting pancreatic beta cells. It accounts for 5% to 10% of patients with diabetes. Intensive insulin therapy is the treatment of choice, but is associated with increased risk of life-threatening hypoglycemia episodes. Approximately 10% of patients with type 1 diabetes are extremely sensitive to insulin therapy and lack hormone counter-regulatory measures, thus they suffer from recurrent severe hypoglycemia.

The two current means of restoring sustained normoglycemia without the associated risk of hypoglycemia are to replace islet cells by either whole organ pancreas transplantation or by islet transplantation. Whole organ pancreas transplantation combined with kidney transplantation is an accepted treatment of choice for type 1 diabetic patients with kidney failure; however, this major surgery is technically demanding and associated with serious peri-operative complications and mortality. Islet transplantation is a minimally invasive procedure whereby isolated, purified islets are infused via the portal vein into the liver. In 2000, published one-year results from a pivotal clinical study showed that insulin independence was achieved in seven consecutive non-uremic type 1 diabetic patients using a novel immunosuppressive regimen called the Edmonton protocol.

Objectives

The objective of this report is 1) to assess clinical research evidence on the safety and efficacy/effectiveness of islet transplantation alone (ITA) for patients with non-uremic type 1 diabetes with severe hypoglycemia or hypoglycemia unawareness; 2) to assess research evidence on the comparability of ITA with intensive insulin therapy or whole organ pancreas transplantation in reducing hypoglycemia episodes and restoring insulin independence in this group of patients.

Methodology

A systematic search of the Cochrane Library, PubMed, CRD Databases (DARE, HTA & NHS EED), EMBASE, Web of Science, and CINAHL was conducted to identify all original published systematic reviews, HTA reports, or primary studies from November 2002 to May 2008. The search was limited to English language full text articles and human studies. Relevant library collections and websites of various HTA agencies, research registers, and clinical guidelines were also searched. Two independent researchers performed a methodological quality assessment.

Results

Fourteen primary studies met the inclusion criteria. Eleven case series studies, including the international multicentre study, reported safety and efficacy/effectiveness results. One other study focused on safety outcome only. One prospective, single centre study compared ITA with insulin therapy, but did not focus on patients with severe hypoglycemia or hypoglycemia unawareness. One retrospective, single centre study compared islet transplantation with whole organ pancreas transplantation; however, the comparison was not specifically for ITA and pancreas transplantation alone.

The original Edmonton protocol continues to undergo modifications, which includes new methods for donor pancreas preservation, islet culture prior to transplantation, using islets prepared from a single donor rather than from multiple donor organs, and change of sirolimus and tacrolimus-based immunosuppressive regimen to other drugs such as mycophenolate mofetil.

In terms of safety, procedure-related complications such as intraperitoneal bleeding (in up to 25% of patients) and portal vein thrombosis (in up to 17% of patients) were reported. The risks of these complications were reduced as clinical experience increased and with the use of prophylaxis measures. Elevated liver enzyme levels were observed in the majority of patients, but resolved spontaneously within one month after transplantation. Immunosuppression-related complications, especially abnormal kidney function, are of great concern. Decline in renal function following the use of sirolimus and tacrolimus was reported in up to 50% of the patients. This sometimes led to discontinuation or change of the original immunosuppressive regimen.

Limited evidence from the 11 case series studies with a total of 208 patients suggested that transplantation of an adequate mass of islet cells (usually from two to three pancreas donors) could restore insulin independence in the short term (one year or less) with adequate glycemic control in 30% to 69% of the patients (44% in the international multicentre trial); however, islet function appeared to deteriorate over time. In the international multicentre trial, only 14% of the patients remained insulin independent at two years. The Edmonton 5-year follow-up study reported that less than 10% of patients remained insulin free at 5 years, while 82% of patients maintained graft function as measured by C-peptide secretion. Partial islet function with reduced insulin requirement provides protection from severe hypoglycemia and improves glycemic control. These results suggest that ITA may be effective in a small group of highly selective patients for whom the benefits of stable glycemia and freedom from hypoglycemia outweigh the potential risks of islet transplantation.

Results from two studies with a total of 109 patients using hypoglycemia measures demonstrated a reduction of fear of hypoglycemia, but improvements in overall health-related quality of life measures were inconsistent. Quality of life tools specific to ITA patients need to be developed.

Preliminary results from two studies with a total of 22 patients showed an improvement in diabetic retinopathy and neuropathy one year after ITA; however, these studies, due to their weak design, are subject to biases and hence preclude any firm conclusion about these outcomes.

No information is currently available on the comparison of ITA with intensive insulin therapy in patients with severe hypoglycemia or hypoglycemia unawareness. No study directly compared ITA with pancreas transplantation alone (PTA) in non-uremic patients. Therefore, it is premature at this time to formulate conclusions about the superiority of one intervention over another.

Conclusions

On the basis of the evidence presented in this report, ITA is an alternative therapeutic option for a small group of highly selective patients (i.e. non-uremic type 1 diabetic patients with severe hypoglycemia and uncontrolled diabetes). Current clinical research demonstrated encouraging short-term efficacy results, including reduced hypoglycemia events, reduced insulin requirements, and stabilized glucose levels. ITA continues to evolve and its role in relation to other therapeutic strategies is still unknown. Based on the current research evidence, it is premature to consider it as 'standard of care' for this group of patients at this time.

ITA currently faces several major obstacles, including the lack of a readily available source of human islets, the need for chronic immunosuppressive therapy, and the loss of insulin independence over time. Future research in exploring more sensitive methods to detect graft loss and elucidate its mechanisms to preserve islet mass over time, developing less toxic immunosuppressive regimens, and finding ways to reduce the number of islets required to reverse diabetes is needed in order to consider islet transplantation as a longer term (more than one year) option.

Alberta is in a unique position worldwide to continue to lead the field of islet transplantation. The lessons learned from islet transplantation will be critical for future cell based therapies (for example, replacement of engineered beta cells or stem cell therapy) for type 1 diabetes.

Reference

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Competing interest

Competing interest is considered to be financial interest, either direct or indirect, that would be affected by the research contained in this report, or creation of a situation where an author's and/or external reviewer's judgment could be unduly influenced by a secondary interest such as personal advancement.

Based on the statement above, no competing interest exists with the author(s) and/or external reviewer(s) of this report.

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ABBREVIATIONS

ACR – albumin to creatinine ratio

AHFMR – Alberta Heritage Foundation for Medical Research

ALT – alanine aminotransferase

AST – aspartate aminotransminase

ATG – antithymocyte globulin

BLA – biologics license application

BMI – body mass index

BT – blood transfusion

CMV – cytomegalovirus

Cr – creatinine

CrCl – creatinine clearance

d(s) – day(s)

DAC – daclizumab

dl – decilitre

DM – diabetes mellitus

eGFR – estimated glomerular filtration rate

ESRD – end-stage renal disease

F – female

FDA – Food and Drug Administration

FU – follow-up

GFR – glomerular filtration rate

HbA1c – glycosylated hemoglobin

HFS – Hypoglycemia Fear Survey

Hr(s) – hour(s)

HRQL – health-related quality of life

HTA – Health Technology Assessment

HTK – Histidine-Tryptophan-Ketoglutarate

IAK – islet after kidney transplantation

ICU – intensive care unit

IE – islet equivalent

IND – investigational new drug

IQR – inter-quarter range

IS – immunosuppression

ITA – islet transplantation alone

Kg – kilogram

L – liter

LP – laparotomy

M – male

MAGE – mean amplitude of glycemic excursion

MeSH – Medical Subject Headings

mg – milligram

ml – milliliter

MMF – mycophenolate mofetil

MRI – magnetic resonance imaging

NA – not available

ng – nanogram

NICE – National Institute for Health and Clinical Excellence

NIH – National Institute of Health

nss – not statistically significant

PAK – pancreas after kidney transplantation

PNE – perinephric edema

PTA – pancreas transplantation alone

PTLD – post-transplantation lymphoproliferative disorder

PVT – portal vein thrombosis

RATG – rabbit antithymocyte globulin

SD – standard deviation

sCr – serum creatinine

SE – standard error

SF-36 – 36-item Short Form Health Survey

SIK – simultaneous islet and kidney transplantation

SIR – sirolimus

SPK – simultaneous pancreas and kidney transplantation

ss – statistically significant

TAC – tacrolimus

U – unit

ULN – upper limit of normal range

UPE – urinary protein excretion

US – United States

UW – University of Wisconsin

wk(s) – week(s)

WOP – whole organ pancreas transplantation

yr(s) – year(s)

GLOSSARY

Autonomic – self-controlling; functionally independent.

Autonomic nervous system – the portion of the nervous system concerned with regulation of the activity of cardiac muscle, smooth muscle, and glands.

Basal C-peptide – a protein that is attached to insulin produced in the body. C-peptide is co-secreted on an equimolar basis with insulin. When the pancreas secrets insulin, C-peptide is released in the blood stream. The C peptide blood levels can indicate whether a person is producing his/her own insulin.

Cold ischemic time – the time measured from the point at which blood flow to the organ is stopped in the donor to the time at which the blood flow to the organ is restored in the recipient.

Creatinine – a waste product from protein in the diet and from the muscles of the body. Creatinine is removed from the body by the kidneys; as kidney disease progresses, the level of creatinine in the blood increases.

End-stage renal disease – also known as chronic kidney failure. A condition in which patients need dialysis treatment or a transplant due to the lost function of the kidney.

Euglycemia – blood glucose level within the normal range.

HbA1c – glycosylated haemoglobin that provides a measurement of a person's average blood glucose level. Glycosylated hemoglobin is the amount of glucose-bound hemoglobin. As the blood glucose concentration increases, the proportion of the hemoglobin molecules that bind glucose increases.

Hepatic steatosis – also known as fatty liver. In this condition, fat is deposited in liver cells, causing enlargement of the liver cells, and sometimes damage to the cell.

Hyperglycemia – an abnormally increased concentration of glucose in the blood.

Hypoglycemia – an abnormally decreased concentration of glucose in the blood.

Hypoglycemia unawareness – a condition in which moderate to severe hypoglycemia occurs without any warning symptoms. This is largely a consequence of insulin therapy in which recurrent, often silent, hypoglycemia reduces both the awareness of and defence mechanisms against subsequent hypoglycemia.

Insulin – a protein hormone secreted by the beta cells of the pancreatic islets in response to elevated blood levels of glucose and amino acids which promotes the efficient storage and utilization of these fuel molecules.

Liver function test – a blood test that measures the levels of liver enzymes (alanine aminotransferase, aspartate aminotransminase) in the blood as a way of helping diagnose liver problems.

Microalbuminuria – the appearance of low but abnormal levels (≥30 mg/day or 20 µg/min) of albumin in the urine. Patients having microalbuminuria are referred to as having incipient nephropathy.

Neuroglycopenia – symptoms and signs of neurological dysfunction that are secondary to hypoglycemia. Prolonged neuroglycopenia can result in permanent brain damage.

Non-uremic – without kidney failure.

Severe hypoglycemia – an episode of hypoglycemia resulting in coma, seizure, or sufficient neurological impairment so that the patient is unable to initiate self-treatment.

Pancreatic islets – irregular microscopic structures scattered throughout the pancreas and comprising its endocrine portion. In humans, they are composed of at least four types of cells: the *alpha cells*, which secrete the hyperglycemic factor glucagon; the *beta cells*, which are the most abundant and secrete insulin; the *delta cells*, which secrete somatostatin; and the *PP (or F) cells*, which secrete pancreatic polypeptide.

TABLE OF CONTENTS

Tables

SCOPE OF THE REPORT

In April 2003, the Health Technology Assessment Unit at the Alberta Heritage Foundation for Medical Research (AHFMR) published a report that assessed scientific evidence on the safety and efficacy of islet transplantation alone (ITA) for non-uremic type 1 diabetic patients who have severe hypoglycemia or uncontrolled diabetes despite compliance with an insulin regimen.[1] On the basis of limited evidence from four case series studies that reported on the clinical experience of three clinical islet transplant centres in Canada (Edmonton), Germany, and the United States, the 2003 AHFMR report concluded the following:

- ITA is effective in controlling labile diabetes and protects against unrecognized hypoglycemia in highly selected patients in the short term. The long-term effects of ITA on metabolic control remain to be proven.
- ITA for non-uremic type 1 diabetic patients with severe hypoglycemia or uncontrolled diabetes is still an evolving procedure with promising results and not considered 'standard of care' at this stage for this group of patients.

The Alberta Ministry of Health recently requested an update on new information and evidence that has emerged since the 2003 AHFMR report.[1] In response to this request, a systematic review was conducted to present any new published evidence on the longer-term (defined as one year or longer) safety and efficacy of ITA using the Edmonton protocol or modifications of the Edmonton protocol.

This report attempts to address the following questions:

- Is ITA a safe procedure for non-uremic type 1 diabetic patients in terms of procedure- and immunosuppression-related adverse events both in the short and longer term?
- Is ITA effective in achieving insulin independence, improving glycemic control, and reducing hypoglycemia episodes over the longer-term?
- Is ITA effective in improving health-related quality of life and reducing secondary complications of diabetes?
- Is ITA comparable to intensive insulin therapy or whole-organ pancreas transplantation in terms of safety and efficacy?

BACKGROUND

The disease – type 1 diabetes

Diabetes mellitus is a chronic metabolic disorder characterized by the presence of hyperglycemia due to absolute or relative insulin deficiency.[2,3] Type 1 diabetes, previously known as insulin-dependent or juvenile onset diabetes

and usually diagnosed in children or adolescents, is primarily a result of progressive destruction of the insulin secreting pancreatic beta cells. The destruction of beta cells can be caused by an autoimmune-mediated process or by unknown mechanisms.[2,4]

As the disease progresses, many patients develop secondary complications from 5 years after diagnosis onward, which include cardiovascular disease (heart disease, hypertension, and stroke), nephropathy (kidney failure requiring dialysis and kidney transplantation), neuropathy (reduced sensation in extremities, gastroparesis, and amputation), and retinopathy (leading to blindness).[5-7]

A small group of type 1 diabetic patients is characterized by a severe instability of glycemic values with frequent and unpredictable hypoglycemia or ketoacidosis episodes.[8] This clinical condition is known as brittle diabetes. The health-related quality of life worsens significantly in these patients because of the frequency of acute events and hospital admissions and to early recurrence of chronic complication.[8]

Many patients also develop abnormalities in the counter-regulatory responses that normally prevent, limit, or reverse hypoglycemia.[9] Within 5 years of diagnosis, many type 1 diabetic patients lose the ability to secret glucagon (a hormone produced by the alpha cells of the pancreas that increases the concentration of glucose in the blood) during hypoglycemia and develop secondary deficits in the other hormonal responses, particularly in adrenaline release (for characteristic warning symptoms such as palpitations and sweating).[9] The combination of defective counter-regulation and symptomatic unawareness of a falling blood glucose significantly increases the risk of suffering episodes of severe hypoglycemia and death.[9]

Epidemiology

The World Health Organization estimated that approximately 171 million people worldwide had type 1 or type 2 diabetes in 2000 and expected that this number will be increased to 366 million by 2030.[10,11] In 2005, a total of 1,325,120 Canadians (12 years or older) were living with type 1 or type 2 diabetes.[12] In the United Stated, the number of people with diagnosed diabetes was estimated to be 10.4 million in 1998.[13]

Type 1 diabetes accounts for 5% to 10% of patients with diabetes. The estimated global annual increase in incidence of type 1 diabetes was 3.0% from 1960 to 1996.[14] In 2003, approximately 430,000 children aged 0 to 14 years had type 1 diabetes worldwide.[15] In the United States, over 30,000 new cases of type 1 diabetes are diagnosed every year.[16]

Treatment

Exogenous insulin therapy

Intensive exogenous insulin therapy remains the primary component of standard of care for the current management of patients with type 1 diabetes. Although this therapy has been proven to delay the progression of chronic diabetic complications, it is associated with increased risk of life-threatening hypoglycemia episodes.[9,17,18] The main factor contributing to this risk is the absolute or relative excess of insulin that results from the currently available insulin regimens.[5,9]

Approximately 10% of patients with type 1 diabetes are extremely sensitive to insulin therapy and lack counter-regulatory measures; this subgroup of patients are thus prone to recurrent severe hypoglycemia.[3] Patients who have lost their ability to demonstrate warning symptoms (sweating, tremor, and tachycardia) during hypoglycemia episodes can develop dizziness, confusion, and blurred vision.[3,18] In severe cases, uncontrolled hypoglycemia can lead to coma, seizure, or even death.[3]

Beta cell replacement

Replacing islet cells either by whole organ pancreas transplantation or by islet transplantation are the two current means of restoring sustained normoglycemia without the associated risk of hypoglycemia.[19] The major benefit of restoring beta cell function is that it allows more physiologic control of glucose metabolism, i.e. glucose dependent insulin secretion, than does exogenous insulin therapy.[20]

Whole organ pancreas transplantation

Whole organ pancreas transplantation combined with kidney transplantation is considered the therapy of choice for type 1 diabetic patients with kidney failure.[8] In these patients, the pancreas was transplanted either at the same time as the kidney (simultaneous pancreas and kidney transplantation, SPK) or in a later operation (pancreas after kidney transplantation, PAK). An estimated 26,571 pancreas transplants were performed worldwide by 2006 (personal communication, Barbara Bland, International Pancreas Transplant Registry, September 2007). Transplant of a pancreas together with a kidney has positive effects on hypoglycemia, kidney complication, and hypertension.[21]

Over the past decade, pancreas transplantation alone (PTA) has been used selectively in some non-uremic type 1 diabetic patients who had a history of frequent and severe metabolic complications, and severe and incapacitating clinical and emotional problems with using insulin injections, or consistent failure of insulin-based management to prevent acute complications.[22] The usual and most persuasive indications for PTA are very poor glucose control and dangerous episodes of hypoglycemic unawareness.[23]

Pancreas transplantation is effective in restoring normal endogenous insulin secretion, maintaining long-term glucose homeostasis, controlling acute and chronic complications of diabetes, and improving quality of life.[5,24,25] The procedure's success is highly dependent on the centre's experience, with an insulin independence rate up to 90% one year,[26] and 60% 3 years post transplant.[8] This procedure, however, is technically demanding and associated with serious peri-operative complications and mortality despite refined surgical techniques, effective immunosuppression modalities, anti-viral prophylaxis, and post transplant monitoring.[27-29] Other limitations include organ availability and poorer graft survival if re-transplantation is needed (unless re-transplantation is immediate because of technical failure of the first transplantation).

Islet transplantation

Clinical islet transplantation, a much less invasive procedure, has been investigated since the early 1970s. Islet transplantation is performed simultaneously with kidney transplantation (SIK), or after kidney transplantation (IAK) for patients with end-stage renal disease (i.e., uremic patients), or alone (ITA) for patients without end-stage renal disease. Clinical islet transplantation involves islet preparation, islet infusion, and a lifetime immunosuppressive regimen.[28] Despite the differences in selecting patient groups (uremic or non-uremic) and performing kidney transplantation, SIK, IAK, or ITA involves the same islet preparation and transplantation procedures. This report focuses only on ITA.

ISLET TRANSPLANTATION PROCEDURE

General information

Islet preparation

Pancreas procurement and preservation

The first stage of islet transplantation is the procurement of a high-quality donor pancreas.[16] Typically, the pancreas is procured from a cadaveric heart-beating, brain dead donor, preserved in University of Wisconsin (UW) solution, and transported to an islet isolation laboratory, ideally within 6 hours.[17,30] The use of a two-layer method (continuously oxygenated perfluorocarbons with standard UW solution) has been proposed to extend the acceptable cold ischemia time[30] and has previously been employed in some centres.[16]

Islet isolation and purification

Islet isolation is a time consuming procedure required to separate the islet from the exocrine component of the pancreatic gland.[16] Upon arrival at the islet isolation laboratory, the pancreas is disassembled using a purified enzyme blend containing collagenase and serine-protease inhibitor.[17] Delivery of collagenase

enzymes injected down the pancreatic duct cleaves the islets from their acinar-islet interface; this approach was recently refined further to allow precise control of the temperature and perfusion pressure.[24] The distended pancreas is then cut into smaller pieces and placed in a semi-automated digestion chamber (known as the Ricordi chamber) and further dissociation is accomplished when the collagenase solution is circulated at 37ºC through the chamber.[17] Islet purification is based on the density differences between acinar and islet cells.[16]

The islet isolation procedure itself causes loss of islet mass because of the destructive activity of the enzymes.[16] Moreover, the donor's characteristics, such as age, cause of death, length of ischemia, and medical status, also affect the quality of the islets.[16]

Before being released for clinical use, the isolated islets have to be rigorously tested for safety, characterization, control of the manufacturing process, and reproducibility and consistency of product lots, according to the guidelines for cellular and tissue-based products established by the United States Food and Drug Administration (US FDA) Centre for Biologics Evaluation and Research.[17]

The cost of building a new, state-of-the-art islet facility in compliance with the US current Good Manufacturing Practice has been estimated as being between US $1 million and $2 million. The cost for one islet isolation and purification procedure varies between $10,000 and $20,000 US.[31] Considering that approximately 50% of processed pancreata result in a transplantable preparation and that most patients require two islet infusions to achieve insulin independence, the isolation-related costs for one patient (using four donor pancreata) could be between $40,000 and $80,000 US.[31]

Because of the technical challenges and cost of the islet isolation and purification procedure and the associated steep learning curve, some clinical centres have chosen to use islets prepared at another centre that has the required expertise and capacity.[31]

Islet infusion

The optimal implant site for islet transplantation has not yet been defined. There is general agreement however that the site should provide adequate microenvironment, vascularization, and nutritional support to maximize the chances for a good islet cell engraftment and to minimize morbidity.[16] The liver, reached via the portal vein, is the most commonly used site.

The islets are implanted into the portal system of the liver using minimally invasive interventional radiological techniques. Percutaneous hepatic cannulation is the standard approach.[16] Islets are infused through the tube by gravity flow from an infusion bag or syringe. The risk of significant hemorrhage and portal vein thrombosis after percutaneous islet transplantation are the major concerns. Rise in liver enzymes and puncture of the gallbladder are also possible events associated with the transplant procedure.[16]

Immunosuppressive therapy

One of the crucial components in the clinical islet transplantation program is the life-long use of immunosuppressive regimen to ensure survival of the allograft by addressing autoimmunity and allorejection. Before 1999, the majority of islet transplantation was performed either in conjunction with or after kidney transplantation; therefore, mainstay immunosuppression was largely based on the protocols used for renal grafts, i.e., the combination of glucocorticoids, anti-metabolites, and calcineurin inhibitors (cyclosporine, tacrolimus), with anti-lymphocyte globulin induction.[17,24] Under these protocols, fewer than 10% of patients were able to discontinue insulin therapy for longer than one year.[24]

Experts in the field reviewed cumulative world experience in clinical islet transplantation performed before 1999. Several key factors were identified that could contribute to the failure in the majority of cases. These factors include: (1) inadequate islet transplant mass; (2) inadequate islet potency; (3) inadequate prophylaxis against allograft rejection or autoimmunity; and (4) routine use of toxic and diabetogenic immunosuppression (e.g., glucocordicoids) after transplantation.[29]

A new protocol implemented in 1999 in Edmonton (known as the Edmonton protocol) was designed to systematically address each of these factors.[29] In 2000, Dr. Shapiro and colleagues published their landmark study[32] in which a 100% one-year insulin independence rate was achieved in seven consecutive non-uremic patients with type 1 diabetes following ITA using the Edmonton protocol.

The Edmonton protocol – A procedural turning point

The original Edmonton protocol is characterized by the following features:[24]

- selection of patients with life-threatening hypoglycemia episodes, hypoglycemia unawareness, and brittle diabetes but without end-stage renal disease;
- delivery of an adequate number of viable islet cells (minimum 10,000 islet equivalent/kg, usually from two to four donors);
- preparation of islet cells in xenoprotein-free medium, limitation of prolonged cold ischemia, and transplantation of freshly harvested islet cells without culture; and
- a less diabetogenic, glucocorticoid-free immunosuppression regimen consisting of induction with daclizumab (anti-interleukin-2 receptor monoclonal antibody) and maintenance with low dose tacrolimus and high dose sirolimus.

Since the reporting of the initial success of the Edmonton protocol, many clinical centres worldwide have initiated or continued islet transplant programs. An estimated 652 patients were treated with islet transplantation (including

ITA, IAK, and SIK) at 47 institutions worldwide between 1999 and 2005.[29] The US National Institute of Diabetes and Digestive and Kidney Disease established the Collaborative Islet Transplant Registry in September 2001.[33] From 1999 to 2005, 21 islet transplant programs in North America have conducted 593 islet infusion procedures in 318 recipients.[34] A 2-year, international, multicentre trial (six centres in North America: Boston, Edmonton, Miami, Minneapolis, Seattle, and St. Louis; and three centres in Europe: Geneva, Giessen, and Milan) was initiated in 2001 to replicate the results obtained by the Edmonton team.

Some clinical practical difficulties have been encountered during the widespread adoption of the Edmonton protocol over the last few years.

First, the requirement of adequate islets prepared from two to four donors limits the widespread use of the Edmonton protocol. Restoration of insulin independence needs to be achieved with a single donor to reduce the risks and costs and to increase the availability of islet transplantation.[35]

Second, transplantation of fresh islets immediately after isolation is not possible for those clinical centres where there is no capacity to prepare islets from donors.[7] Islets prepared by remote centres have to be shipped to these centres; therefore, cultured rather than fresh islet cells have to be used.[36]

Third, the introduction of sirolimus represents a key component to the development of steroid-free immunosuppression in the Edmonton protocol.[37] However, sirolimus and tacrolimus are associated with nephropathy, hyperlipidemia, and anemia, all potentially increasing cardiovascular risk in the long term.[38]

Finally, the original Edmonton protocol applied very stringent patient selection criteria. Only a small portion of patients with type 1 diabetes would therefore be suitable candidates for the Edmonton protocol.[37]

Post-Edmonton modifications

In addressing the clinical issues mentioned above, significant efforts have been made to improve the safety and efficacy of the original Edmonton protocol. These include:

- **Islet preparation:** use of a two-layer oxygenated perfluorodecalin for pancreas protection during transportation[24] and, recently, use of the Histidine-Tryptophan-Ketoglutarate (HTK) solution (Dr. Tatsuya Kin, personal communication, August 2008).
- **Islet culture:** use of cultured islets rather than fresh islets to ensure the quality of islet cell products while also allowing additional time for patient preparation, possible pre-transplant interventions, and the opportunity to ship processed islets to remote sites for transplantation,[24,30,39] as well as the possibility for the procedure to take place at a planned time when experienced personnel are available (Dr. Senior, personal communication, August 2008).

- **Single donor:** use of islets prepared from a single donor to achieve insulin independence. Essential strategies identified to promote the engraftment and functional survival of transplanted islets from a single donor include limiting ischemic injury of islets during pancreas storage, culturing islets to allow pre-transplant initiation of immunosuppression, and tailoring the induction of immunosuppression to target both alloimmunity and autoimmunity.[24,35,40]
- **Islet infusion:** use of an infusion bag rather than a syringe for islet delivery to further improve the sterility and safety of the procedure.[3,24] Physical and mechanical ablation of the catheter tract using combinations of coils and thrombostatic agents to reduce the risk of bleeding following percutaneous transhepatic access to the portal vein.[24]
- **New immunosuppressive agents:** use of other medications such as mycophenolate mofetil (MMF) to avoid the side effects of sirolimus. In addition to the immunosuppressive regimen, additional medications that are biologic or immunomodulatory are also being investigated; for example, inflixumab is given before islet transplantation to decrease inflammation to achieve increased islet survival.[16]

Metabolic monitoring of islet graft

Transplanted islets can be destroyed during early or late phases; however, mechanisms of islet destruction are poorly understood. Early islet loss may occur during the isolation procedure or in the graft microenvironment within the liver, through ischemia-reperfusion-like injury and non-specific inflammatory phenomena. An acute inflammatory process that instantly destroys a large part of intraportally injected islets upon contact with blood was described recently and it is thought to be a major determinant of early islet graft loss.[41]

Factors contributing to late islet graft loss may include allogeneic rejection, recurrence of autoimmunity, islet toxicity of the immunosuppressive drugs, lack of beta cell regeneration because of the antiproliferative properties of sirolimus, or "exhaustion" of the islet graft.[41]

Current clinical monitoring of islet grafts is based on metabolic islet function and utilizes serum markers in the basal and stimulated states (Table 1).[41] According to measurement of these markers, islet grafts can be classified as being fully functioning (insulin independent), partially functioning (insulin required and detectable C-peptide), or not functioning (no detectable C-peptide).

Currently, clinical investigators lack monitoring tools that can detect graft damage or a decrease in graft mass or function in a timely manner. The major problem with metabolic tests is that they are not early markers of islet graft dysfunction and generally appear when it is probably no longer possible to salvage a failing graft. Monitoring of acute and chronic rejection is very important, but efficient tools to monitor islet rejection are currently lacking.[41]

New techniques of islet graft monitoring need to be developed to better understand when and how islet grafts are damaged, and to detect islet damage early enough to allow for appropriate intervention to salvage the graft.[41]

Table 1: Metabolic measurement of islet function

Overall function	Plasma glucose
	Plasma insulin
	Plasma C-peptide
	HbA1c, fructosamine
	Insulin requirement
	Secretory Unit of Islet Transplant Objects
	Beta-score
Glucose stability	Mean Amplitude of Glycemic Excursions
	Lability Index
	Continuous Glucose Monitoring Systems
Stimulation tests	Arginine stimulation test
	Glucagon stimulation test
	Mixed meal tolerance test
	Oral Glucose Tolerance Test
	IV Glucose Tolerance Test
	Glucose-potentiated arginine stimulation test

Source: Adapted from Berney & Toso 2006[41]

REGULATORY STATUS

Health Canada

In June 2007, Health Canada released a new regulatory framework entitled *Safety of Human Cells, Tissues and Organs for Transplantation Regulations*, which is administrated by the Biological and Genetic Therapies Directorate, Health Products and Food Branch.[42] Use of allogeneic islet cells for transplantation should follow these regulations in terms of processing, storage, record keeping, distribution, importation, error, accident, and adverse reaction investigation reporting.[43]

US Food and Drug Administration (FDA)

In the United States, allogeneic pancreatic islets meet FDA criteria for regulation as both a drug product and a biologic product; therefore, islets cannot be used clinically without an investigational new drug (IND) application or an approved

biologics license application (BLA).[44] Allogeneic islets are considered a somatic cell therapy and will require an approved BLA before they can be marketed for treatment of patients with diabetes. Islet transplantation has not been approved for marketing by the US FDA because of the current lack of information showing the safety, purity, potency, and effectiveness of the final product.[44] Currently, the use of allogeneic islets for the treatment of type 1 diabetes is investigational and is only used in clinical trials under IND application.[44]

Furthermore, the classification of islet cells as a biologic mandates that any centre that harvests or processes islets from cadaveric donors develop and maintain a facility regulated as a "manufacturing facility" under the current Good Manufacturing Practices and monitoring processes for all such facilities.[45]

DESCRIPTION AND METHODOLOGICAL QUALITY OF STUDIES

A detailed description of the approach used for the literature search, study selection, methodological quality assessment, data extraction, and data synthesis is provided in Appendix A (Methodology). For a study with multiple publications, the most recent publication was included as a key study with supplemental information from other relevant publications being mentioned when necessary.

Description of included studies

A comprehensive literature search (see Appendix A: Methodology/Search strategy) identified 14 primary studies that met the inclusion criteria (Appendix A: Methodology/Study selection). Eighty studies were excluded and the main reasons for exclusion are listed in Appendix B.

Of the 14 primary studies, 11 case series studies[27,35,46-54] reported clinical outcomes on a total of 208 patients (mean age ranged from 33 to 50 years), which included the international multicentre study of 36 patients,[46] the most recent update of the Edmonton group on 65 patients,[47] and the European multicentre study of 10 patients.[53] These 11 studies are the main source of evidence on safety and efficacy of ITA for type 1 diabetes and are referred to as key studies hereinafter. One study[55] only examined the safety issues of islet transplantation. One retrospective study[23] compared islet transplantation with whole organ pancreas transplantation and another study with two publications[56,57] compared islet transplantation with intensive medical therapy.

Nine articles focused on the different outcomes, for example safety,[58-63] health-related quality of life measures,[64,65] or secondary complications[66] in the patients who were included in the key studies. The results from these articles are presented in the text or the tables, but these articles are not counted as the key studies.

The second annual analysis of the Collaborative Islet Transplant Registry,[67] published in 2007, focused on 118 patients who received ITA between January

1999 and December 2004. Insulin independence was achieved in 67.0% at 6 months and 58.0% at 12 months following the last infusion. The occurrence of severe hypoglycemia episodes decreased from 82% of included patients prior to islet transplantation to 2% at one and 12 months after last infusion. This analysis was not included in this report because many of the patients in the registry were also enrolled in the selected key studies for this review.

Methodological quality of the selected studies

Although case series studies are generally considered as the lowest level of evidence, findings from this type of study are the main source of information about the safety and efficacy of islet transplantation. A critical appraisal of some important aspects of a case series study may be helpful in identifying the methodological strength and weakness of each study and allowing more certainty in the conclusions based on the research findings.

A critical appraisal of methodological quality using an 18-item checklist was conducted for the 11 key case series studies that reported on both safety and efficacy outcomes. The method used to assess the methodological quality is described in Appendix A (Methodology/Methodological quality assessment). The quality assessment checklist and the assessment results are presented in Appendix C. Five of the 18 criteria are considered most important in the context of islet transplantation. The results on these five criteria, along with the overall total score based on all criteria met for each study, are presented in Table 2.

Table 2: An overview of quality assessment results

Study	Multi-centre	Consecutive patients	Before and after measurement	Length of follow-up	Lost to follow up	Total score
International[46]	√	x	√	√	√	15*
Edmonton[47]	x	√	√	√	√	14*
Miami[48]	x	x	√	√	√	14*
Minnesota[35]	x	√	√	√	√	16*
Minnesota[49]	x	x	√	√	√	16*
NIH[27]	x	x	√	√	√	10
Houston[50]	x	x	√	√	√	12
Milan[51]	x	x	√	√	√	14*
Brussels[52]	x	√	√	√	√	14*
Swiss-French GRAGIL group[53]	√	x	√	√	√	15*
Australia[54]	x	x	√	√	√	12

* ≥ 75% of the total score of 18

As shown in Table 2, among the 11 key studies, eight studies[35,46-49,51-53] received a score of 14/18 or above (≥ 75% of the total score).

When looking at the five most important criteria, only two of the trials were multicentre trials,[46;53] indicating that generalizability of the findings from the majority of the studies is in question. Furthermore, only three studies[35,47,52] enrolled consecutive patients, suggesting that selection bias could not be minimized in most of the studies. On the other hand, in all 11 studies, outcomes were measured before and after the intervention and the length of follow up as well as lost to follow up were reported consistently. From Table D.1 in Appendix D, the majority of studies provided sufficient details on patient characteristics and intervention, and defined outcome measures a priori. These results demonstrated an overall adequate reporting of the most important aspects; therefore no studies were excluded based on the quality assessment.

RESULTS

Safety

Islet transplantation is associated with procedure-related and immunosuppression-related complications. Detailed safety data from the 11 key studies is presented in Appendix D: Table D.1. Additional safety data from another seven articles is presented in Appendix D: Table D.2.

Procedure-related complications

None of the studies reported any peri- or post-operative deaths that occurred as a direct consequence of the ITA procedure.

Acute intraperitoneal bleeding, portal vein thrombosis (mostly partial), and liver abnormality (increase in liver enzymes or presence of hepatic steatosis on imaging test) following the ITA procedure were observed in the majority of the studies (Table 3).

Table 3: Procedure-related complications

Centre	No. of patients	Intraperitoneal Bleeding	Portal vein thrombosis	Liver abnormality
International multicentre[46]	36	7/77 procedures (9%) (BT: 4, LP: 1)	Complete: 0 Partial: 2/36 pts (6%)	Liver enzyme: NA Hepatic steatosis on MRI: 4/13 pts (31%)
Edmonton[47]	65	15/65 pts (23%) (BT: 7 occasions, LP: 2 pts)	Partial: 5/65 pts (8%)	AST elevation: 78% of procedures Hepatic steatosis on MRI: 8/36 pts (22%)
Miami[48]	16	2/34 procedures (6%) (BT: 1)	0	Liver transaminase elevation: 34/34 procedures (100%) Hepatic steatosis on MRI: 1/13 pts (8%)
Minnesota[35]	8	0	0	NA
Minnesota[49]	6	0	0	AST elevation: 4/6 pts (67%)
NIH[27]	6	1/6 pts (17%) (BT)	Partial: 1/6 pts (17%)	NA
Houston[50]	11*	0*	0*	ALT elevation: 11/11 pts* (100%)
Milan[51]	14†	3/14 pts (21%)†	Partial: 1/14 pts (7%)†	AST & ALT elevation: 10/14 pts (71%)†
Brussels[52]	24	0	0	ALT elevation: 8/24 pts (33%)
Swiss-French GRAGIL group[53]	10	1/10 pts (10%)	Partial: 1/10 pts (10%)	Liver transaminase elevation: 1/10 pts (10%)
Australia[54]	6	1/6 pts (17%) (BT and LP)	Complete: 1/6 pts (17%) (withdrawn from the study) Partial: 1/6 pts (17%)	ALT elevation: 6/6 pts (100%) Hepatic steatosis on ultrasound: 2/6 pts (33%)

Bolded are rates based on procedures

* Data from an earlier publication by Barshes et al. 2005[68]

† Data from an earlier publication by Bertuzzi et al. 2004[69]

ALT: alanine aminotransferase; AST: aspartate aminotransaminase; BT: blood transfusion; LP: laparotomy; MRI: magnetic resonance imaging; NA: not available; No.: number; pts: patients

Bleeding

As shown in Table 3, 7 of the 11 studies reported occurrence of intra-peritoneal bleeding in up to 9% of the procedures; most of them required either blood transfusion or laparotomy. The Edmonton study reported bleeding in 15 out of 65 patients (23%).[47] In this study, most of the 15 major bleeding episodes occurred in the early recruited patients. According to the authors, the risk of bleeding was recently resolved by effective sealing of the portal catheter tract and by discontinuation of aspirin 2 weeks before transplantation.

One follow-up study of the Edmonton series[58] reported that, of 132 ITA procedures performed on 67 patients, 18 bleeding events (14% of 132 total procedures) occurred in 17 patients (25%); three of these patients required surgical treatment (Table D.2). The data from the two tables indicated that intra-peritoneal bleeding occurred in up to 14% of the total procedures or in up to 25% of the patients.

Portal vein thrombosis

In six of the 11 key studies, portal vein thrombosis occurred in 6% to 17% of the patients following ITA procedure. Both the international study[46] and the Edmonton study[47] reported branch portal vein thrombosis; all patients were treated successfully with anticoagulation. In the Australian study,[54] one patient developed right portal vein thrombosis after the first islet infusion and was withdrawn from the study.

Liver abnormality

A transient elevation of liver enzyme following ITA appeared to be a common phenomenon. Eight of the 11 key studies reported increase in liver enzyme following ITA procedure, with the event occurring in 10% to 100% of the patients. Liver enzyme elevation usually peaked (2.5 to 5 times of upper limit of normal range) at the first week post-transplant and gradually decreased in the second and third weeks. The response is self-limiting and resolves spontaneously within one month after transplantation without any clinical consequences.

The exact cause for elevated liver enzyme remains unclear. Many factors may be involved, including hypoxic injury to the presinusoidal hepatocytes after islet embolization, injurious inflammatory reaction triggered by islet injection into the liver through the portal vein, and endotoxin contamination of reagents used in islet isolation and purification.[70]

Only four of the 11 key studies and another study[59] assessed the presence of hepatic steatosis (fatty liver) with either magnetic resonance imaging or ultrasound; this was done in only a proportion of the total number of patients in the international multicentre trial (13 of 36 patients) and the Edmonton study (36 of 65 patients). Hepatic steatosis may be attributed to intra-hepatic insulin secretion; however, its clinical significance remains unknown.

In summary, serious procedure-related adverse events such as intra-peritoneal bleeding and portal vein thrombosis occurred in a considerable proportion of patients (up to 25% and up to 17%, respectively), but these were treated successfully. Elevation of liver enzymes following ITA is a common finding (up to 100% of patients), but this is a self-limited process and usually returns to normal within one month.

Immunosuppression-related complications

Immunosuppressive therapy is associated with many different types of complications involving the hematological, cardiovascular, respiratory, renal, neurologic, and immune systems. Data on immunosuppression-related complications reported in all case series studies are tabulated in Appendix D. Since deterioration of kidney function following immunosuppressive therapy is of great clinical concern, data reported in the 11 key studies on kidney function and changes or withdrawal of immunosuppressive regimen due to their side effects reported are summarized in Table 4.

Table 4: Immunosuppression-related complications

Centre	Renal function	Immunosuppressive regimen
International multicentre[46] N = 36	Albuminuria: 13/36 pts (36%) sCr/CrCl: modest decline in CrCl with a mild elevation of sCr over time	Medication: DAC, SIR, TAC Change: 9/36 pts (25%) Discontinuation: 2/36 pts (6%)
Edmonton[47] N = 65	Albuminuria: 8/47* pts (17%) (5 from microalbuminuria to macroproteinuria; 3 from normal to microalbuminuria) sCr/CrCl: decline in CrCl with an elevation of sCr over time	Medication: DAC, SIR, TAC Change: 10/43† (23%) Discontinuation: NA
Miami[48] N = 16	Albuminuria: 5/16 pts (31%) macroalbuminuria sCr: increased in 2/16 pts (13%)	Medication: DAC, SIR, TAC Change: 4/16 pts (25%) Discontinuation: 3/16 pts (19%)
Minnesota[35] N = 8	No change in CrCl, no albuminuria	Medication: RATG, methylpredisolone, DAC, etanercept, SIR, MMF, TAC Change/discontinuation: none
Minnesota[49] N = 6	Albuminuria: 2/6 pts (33%) (1 from normal to macroalbuminuria; 1 from micro- to microalbuminuria)	Medication: hOK3γ (Ala-Ala), SIR, TAC Change/discontinuation: NA
NIH[27] N = 6	Renal function worsening in 3/6 pts (50%)	Medication: DAC, SIR, TAC Change: 1/6 pt (17%) Discontinuation: 2/6 pts (33%)
Houston[50] N = 12	Proteinuria: 0	Medication: DAC, SIR, TAC Change/discontinuation: NA

Table 4: Immunosuppression-related complications (continued)

Centre	Renal function	Immunosuppressive regimen
Milan[51] N = 19	Proteinuria: worsened in 4/19 pts (21%) sCr/CrCl: sCr increased and CrCl decreased in 2/19 pts (11%) (progressed to ESRD)	Medication: DAC, SIR, TAC, MMF Change: 7/19 pts (37%) Discontinuation: 4/19 pts (21%)
Brussels[52] N = 24	Albuminuria: improved in 8/8 pts (100%) with pre-transplant albuminuria sCr: decreased 16%	Medication: ATG, MMF, TAC Change: NA Discontinuation: 1/24 pts (4%)
Swiss-French GRAGIL group[53] N = 10	NA	Medication: DAC, SIR, TAC Change: 1/10 pts (10%) Discontinuation: 0
Australia[54] N = 6	GFR: decreased significantly in 1/6 pts (17%)	Medication: DAC, SIR, TAC Change: 1/6 pts (17%) Discontinuation: 1/6 pts (17%)

* data only available for 47 pts. † Data only available for 43 pts.

ATG: antithymocyte globulin; CrCl: creatinine clearance; DAC: daclizumab; ESRD: end-stage renal disease; GFR: glomerular filtration rate; N: total number; NA: not available; pt(s): patient(s); sCr: serum creatinine; SIR: sirolimus; TAC: tacrolimus

Changes in renal function

As shown in Table 4, 7 of the 11 key studies reported a decline in renal function following ITA in 17% to 50% of patients, reflected by an increase in albuminuria or proteinuria, elevation in serum creatinine level, or decline in creatinine clearance. In the Milan study,[51] two patients with pre-transplant kidney impairment progressed rapidly to end stage renal disease, despite discontinuation of immunosuppressive therapy.

Two other studies[55,61] that assessed only the safety aspects of the intervention focused on changes in renal functions after ITA (Table D.2). The study by Senior et al.[61] was the first systematic report of changes in renal function following clinical ITA. This subgroup analysis of 41 Edmonton cases found that ITA was associated with a decline in estimated glomerular filtration rate (in 47% of patients at one year and 80% of patients at 4 years) and progression of albuminuria in 20% of patients, despite sustained improvements in glycemic control.

Changes in immunosuppressive regimen

As shown in Table 4 and Table D.1, seven key studies reported that in 10% to 37% of patients (25% in the international multicentre study and 23% in the

Edmonton study), the initial immunosuppressive regimen (mostly with high-dose sirolimus and low-dose tacrolimus) had to be switched to an alternative immunosuppressive regimen due to side effects. In most cases, MMF replaced sirolimus or tacrolimus because of the renal toxicity of the latter two. In some cases, the doses of sirolimus, tacrolimus, or MMF had to be reduced.

Six key studies reported that in 4% to 33% of patients, immunosuppressive therapy had to be discontinued due to graft failure or immunosuppression-related complications, including deterioration of renal function, mouth ulcer, diarrhea, nausea, headache, aspiration pneumonia, parvovirus infection, hypereosinophilia, intolerance to immunosuppression, or MMF-caused gastrointestinal symptoms.

In summary, statistically significant decline of renal function in patients was observed in some studies following immunosuppressive therapy, although the clinical significance of this change remains unknown. The decline in renal function might reflect the combined toxic effects of tacrolimus and sirolimus on pre-existing diabetic nephropathy. The original immunosuppressive regimen used in the Edmonton protocol, that is, high-dose sirolimus and low-dose tacrolimus, had to be switched to an alternative immunosuppressive regimen (e.g., MMF) in a significant proportion (10 % to 37%) of the patients because of side effects, most notably kidney impairment.

Other complications

As demonstrated in Table D.1, other types of complications are common. In the international multicentre trial,[46] the most commonly reported non-serious adverse events included mouth ulcers (92%), anemia (81%), leucopenia (75%), diarrhea (64%), headache (56%), neutropenia (53%), nausea (50%), vomiting (42%), acne (39%), and fatigue (39%). This study noted that, while the frequency of mouth ulceration, anemia, and leucopenia was high, the frequency of immunosuppression-related complications was similar to that typically seen in solid organ transplantation. Furthermore, no post-transplantation lymphoproliferative disease (PTLD), cancer, opportunistic infections, or disease related to cytomegalovirus or Epstein-Barr virus occurred in this multicentre study.

Three studies that assessed only the safety aspects of the intervention (Table D.2) reported some immunosuppression-related complications that were not commonly reported in the key studies, including alteration of the female reproduction system,[62] ulceration of the small bowel,[60] and cytomegalovirus (CMV) infection.[63]

Efficacy

Details on patient characteristics, islet transplantation protocols, and outcomes extracted from each of the 11 key studies are tabulated in Appendix D (Table D.1).

Insulin independence

As shown in Table 5, insulin independence rates reported in the 11 key studies varied from 30% to 69% at one year, 14% to 33% at 2 years, and 7.5% at 5 years post-transplant.

Table 5: Insulin independence

Centre	Islet culture	Donor	Immunosuppressive regimen	Insulin independence
International multicentre 2006[46] 36 pts; FU: up to 3 yrs	No	Multiple	DAC, SIR, TAC	16/36 pts (44%) at 1 yr; 5/36 (14%) at 2 yrs
Edmonton 2005[47] 65 pts; FU: up to 5 yrs	Yes	Multiple	DAC, SIR, TAC	7.5% at 5 yrs
Miami 2005[48] 16 pts; FU: up to 3 yrs	Yes	Multiple	DAC, SIR, TAC	11/16 pts (69%) at 1 yr 5/16 (31%) at 2 yrs
Minnesota 2005[35] 8 pts; FU: 1 yr	Yes	Single	RATG, methylpredisolone, DAC, etanercept, SIR, MMF, TAC	5/8 pts (63%) at 1 yr
Minnesota 2004[49] 6 pts; FU: 1 yr	Yes	Single	hOK3γ (Ala-Ala), SIR, TAC	4/6 pts (67%) at 1 yr
US NIH 2003[27] 6 pts; FU: 1 yr	No	Multiple	DAC, SIR, TAC	3/6 pts (50%) at 1 yr
Houston 2005[50] 12 pts, FU: 1 yr	NA	Multiple	DAC, SIR, TAC	6/12 pts (50%) any time
Milan 2007[51] 19 pts; FU: up to 2 yrs	Yes	Multiple	DAC, SIR, TAC, MMF	8/19 pts (42%) at 1 yr
Brussels 2006[52] 24 pts; FU: 1 yr	Yes	Multiple	ATG, MMF, TAC	10/24 pts (42%) at 1 yr
Swiss-French GRAGIL group[53] 10 pt; FU: up to 3 yrs	Yes	Multiple	DAC, SIR, TAC	3/10 pts (30%) at 1 yr
Australia 2006[71] 6 pts; FU: up to 2 yrs	NA	Multiple	DAC, SIR, TAC	1/6 pts (33%) at 1 yr 2/6 pts (33%) at 2 yrs

ATG: antithymocyte globulin; DAC: daclizumab; FU: follow-up; MMF: mycophenolate mofetil; NA: not available; pt(s): patient(s); RATG: rabbit antithymocyte globulin; SIR: sirolimus; TAC: tacrolimus; yr(s): year(s)

One-year insulin independence with adequate glycemic control was the primary endpoint of the international multicentre study.[46] Adequate glycemic control was defined by an HbA1c level of less than 6.5%, with a fasting plasma glucose not exceeding 7.8 mmol/L more than three times in any week, and not exceeding 2-hour postprandial levels of 10 mmol/L more than four times per week. In this study, the original Edmonton protocol was used in 36 patients. Insulin independence at one year after ITA was achieved in 16 (44%) patients (five patients with one transplant and 11 patients with two to three transplants). In this trial, a positive relationship was observed between previous experience with islet transplantation at a centre and the attainment of the primary endpoint. Insulin independence with adequate glycemic control was achieved in 67% of patients at the centres with more experience, compared to only 22% of the patients at the centres with less experience ($P = 0.007$).

In most cases, one-year insulin independence was achieved with two to three islet transplants where one or two donors were required for each transplant. In contrast, two studies conducted in Minnesota[35;49] focused on transplanting islets prepared from a single donor to achieve insulin independence. Pancreas organ donors were eligible only if they were 50 years old or younger. Islets were cultured before transplantation. Each patient only received one transplant with islets prepared from a single donor.

The immunosuppressive regimens used in these two studies were quite different from those used in the Edmonton protocol. The two studies demonstrated that more than half of the included patients achieved and sustained insulin independence, normoglycemia, and freedom from hypoglycemia over one year of follow-up. Factors such as excluding pancreases from donors older than 50 years, limiting cold storage to less than eight hours, using the two-layer preservation method, avoiding use of Ficoll during islet purification, and culturing islets prior to transplantation (permitting initiation of immunosuppression 2 days prior to transplant) could contribute to the success of single-donor islet transplantation in selected type 1 diabetic recipients.

The Edmonton study[47] reported efficacy results from a longer-term (one year or longer) follow-up. At 5-year post-transplant, C-peptide was detectable in 82% of patients; however, only 7.5% of the patients (i.e., one in four patients available at 5 years, Dr. Ryan, personal communication) remained insulin independent. Despite persistent graft survival, the majority of patients had to resume insulin therapy (at a significantly lower dose) in order to maintain good glycemic control. These results indicate that the islet function was significantly reduced over a longer period and was completely lost in a small minority of patients.

Glycemic control

As shown in Table D.1, in all studies, HbA1c levels were reduced following islet transplantation, even with partial graft function. In patients who achieved insulin independence, the HbA1c levels could return to normal ranges. In

patients without insulin independence, the HbA1c levels also significantly reduced with a lower dose of insulin therapy. In the multicentre study, during a follow-up of 24 months, the mean HbA1c levels were under 6.0% in patients who achieved insulin independence and under 7.0% for patients with partial graft function. The Edmonton study[47] demonstrated well controlled HbA1c in those patients who remained off insulin and even in those who resumed insulin but who were C-peptide positive (indicating partial graft function), compared to those who lost all graft function. These results suggest that persistent islet function even without insulin independence could provide the benefits of improved glycemic control.

Hypoglycemia

As demonstrated in Table D.1, in nine key studies that reported results on hypoglycemia, patients who achieved insulin independence were completely free from hypoglycemia episodes. Hypoglycemia episode occurred in some patients who were still on insulin therapy, but with reduced severity because of a decreased insulin requirement.

Health-related quality of life

Information regarding health-related quality of life (HRQL) following ITA was not available in most of the key studies. Two studies, one an earlier publication[64] of the Houston study and the other a recent publication of the Edmonton group,[65] attempted to examine the impact of islet transplantation on health-related quality of life. Both studies used generic HRQL tools to measure overall HRQL and disease-specific tools to measure diabetes-related quality of life.

One study[64] included 10 patients and used two disease-specific questionnaires, the Hypoglycemia Fear Survey and the Fatigue Questionnaire, and one generic questionnaire, the 36-item Short Form Health Survey (SF-36), to measure HRQL before and one year after ITA. This study found that hypoglycemia-related anxiety symptoms and hypoglycemia-induced behaviour modification decreased significantly after ITA. Generic measures of HRQL showed improvement after ITA. However, no significant changes were seen in fatigue-related symptoms.

The other study[65] used a general tool, the Health Utilities Index Mark 2, and a hypoglycemia specific tool, the Hypoglycemia Fear Survey, to measure HRQL before and 3 years after islet transplantation.

Results from 99 islet transplant recipients and 166 controls showed that ITA had no impact on overall HRQL. Fear of hypoglycemia was reduced significantly in ITA recipients up to 36 months post-transplant. Of 43 patients who completed questionnaires both prior transplant and 12 month post-transplant, the decrease in fear of hypoglycemia correlated to the HYPO score, the Lability Index, and the insulin requirement. At one year, patients off insulin experienced less fear of hypoglycemia than those on insulin. These results

demonstrated that fear of hypoglycemia correlated with the occurrence of hypoglycemia, blood glucose stability and insulin requirement.

In summary, both studies showed reduced fear of hypoglycemia after islet transplantation, but the results were inconsistent in terms of overall HRQL.

Secondary complications of diabetes

Two studies[50,66] examined the effects of ITA on secondary complications, including retinopathy and neuropathy.

The Houston study[50] presents the first objective data on the effect of ITA on the progression of diabetic retinopathy and neuropathy. This study of 12 patients demonstrated that all ITA recipients experienced stabilization of their diabetic retinopathy and that 50% of the patients exhibited stabilization or even improvement of their diabetic neuropathy during a one-year follow-up. The authors suggested that studies with a larger patient population and longer follow-up periods (5 years or longer) are needed to ascertain the true benefit of ITA.

An earlier publication of the Milan study[66] used colour Doppler imaging to examine whether ITA improves retinal microcirculation in patients with type 1 diabetes. The study found a statistically significant increase in the blood flow velocities of the recipients' central retinal artery and vein one year after ITA, which may reflect an increase of blood flow (i.e., improved retina microcirculation).

Comparison of islet transplantation with intensive insulin therapy

Only one study[57] was found that attempted to compare the effect of ITA with best medical therapy in patients with type 1 diabetes (Table D.3).

This single-centre, prospective study included patients who had evidence of secondary diabetic complications such as retinopathy or mild nephropathy. In contrast to most other studies included in this report, severe hypoglycemia or hypoglycemia unawareness was not part of the eligibility criteria. Islets prepared from one to three donors were infused. Immunosuppressive regimen consisted of antithymocyte globulin, sirolimus, or MMF, and tacrolimus. The best medical therapy was defined as the control of blood glucose with intensive insulin therapy, blood lipids with statins, blood pressure with antihypertensive agents, and renal protection with angiotensin-converting enzyme inhibitors.

Forty-four patients received the intensive insulin therapy and 21 of them then received ITA. Results from the 21 patients who received ITA with a follow-up of a median 29 months (over a range of 13 to 45 months) were compared with 44 medically treated patients with a median follow-up of 29.5 months (over a range of 13 to 56 months). Seventeen of the 21 ITA recipients became insulin

independent following the procedure; however, longer-term results were not available. HbA1c levels were statistically significantly lower in the ITA group than in the medical treatment group. There was no difference in the rate of decline in measured glomerular filtration rate between the two groups, and this rate did not differ from that expected for the general population.

Comparison of islet transplantation with pancreas transplantation

Frank and colleagues[23] conducted a retrospective analysis of a consecutive series of whole organ pancreas transplantation and islet transplantation performed at a single centre.

Results were compared from 30 patients who received pancreas transplantation (25 SPK and five PAK) and 13 patients who received islet transplantation (nine ITA and four IAK); however, no attempts were made to compare PTA with ITA. The two groups were similar in terms of age, gender, body mass index, and duration of diabetes. However, while 73.3% of the patients in the pancreas transplantation group had a history of dialysis because of end-stage renal disease, none of the patients in the ITA group had such a history. As to the donor pancreata, all pancreata used for islet transplantation were rejected for use in pancreas transplantation, indicating better donor quality for pancreas transplantation than that for islet transplantation.

As indicated in Table D.4, procedure-related complications (e.g., requirement for post-transplant surgery or blood transfusion) were more severe in patients with pancreas transplantations than for patients with ITA. In terms of immunosuppression-related complications, sirolimus-related mouth ulceration was observed in all nine ITA recipients, which led to discontinuation of immunosuppressive regimen in one patient. In contrast, CMV infection was found in three pancreas recipients but not in ITA recipients.

There was no statistically significant difference in patient survival and graft survival between the islet transplantation and the pancreas transplantation groups. Pancreas transplantation was superior to islet transplantation in terms of C-peptide levels, HbA1c levels, and insulin requirements, and in the duration of insulin independence achieved if partially functioning islet grafts were included. However, no efficacy results were reported separately for ITA recipients.

The authors concluded that both pancreas transplantation and islet transplantation proved highly successful at establishing insulin independence in type 1 diabetic patients. Patients who received pancreas transplantation experienced longer lengths of hospital stay, more readmissions, and more post-operative complications, but they exhibited a more durable state of

normoglycemia with greater insulin reserves. In contrast, islet transplantation was associated with less procedure-related morbidity and shorter hospital stays, but achieving insulin independence by islet transplantation proved to be more expensive than pancreas transplantation mainly because of the requirement for multiple donors in order for the patient to gain insulin independence.

The authors suggested that, because donor pancreata that are unsuitable for pancreas transplantation can often be used successfully for islet transplantation, islet transplantation should continue to be evaluated as a complementary alternative rather than as a replacement for the better-established method of pancreas transplantation.

Summary of other HTA reports

Three identified HTA reports[21,45,72] were published after the last search date of the 2003 AHFMR report.[1] The ECRI 2005 report[45] was a meta-analysis, whereas the other two reports, one prepared by the Blue Cross Blue Shield Association in 2004[21] and the other one prepared by the Ontario Ministry of Health and Long-term Care in 2003[72] synthesized research evidence qualitatively. Findings from the three reports are summarized below.

The objectives of the ECRI review[45] were to address:

(1) effectiveness of islet transplantation on exogenous insulin requirements and glucose control;

(2) effects of islet transplantation on secondary complications of diabetes;

(3) comparative efficacy of intensive insulin therapy and islet transplantation; and

(4) morbidity and mortality rates of islet transplantation.

A literature search was conducted to locate studies published before June 2005; therefore this review did not include the results of the international multicentre trial published in 2006.[46] This review assessed the findings from 19 studies conducted at seven clinical centres with a total of 98 patients. All of these studies employed an uncontrolled, case series design. A 25-item questionnaire was used to rate study quality. An algorithm with 12 decision points was used to evaluate the stability and strength of the evidence. Because of the lack of control groups, only some outcomes such as insulin independence and freedom from hypoglycemia were analyzed.

Estimated insulin independence rates were 72% (95% confidence interval 61% to 83%) at any time after transplantation, and 57% at one year after the last transplant (95% confidence interval 22% to 89%). The estimated rate of freedom from hypoglycemia during the follow-up periods (ranging from 3 to 33 months) was 97% (95% confidence interval 87% to 100%).

Estimated rates for procedure-related adverse events were 8% (2% to 18%) for branch portal vein thrombosis and 8% (2% to 17%) for bleeding requiring blood transfusion. Estimated rates for immunosuppression-related adverse events were 92% (75% to 100%) for mouth ulcers, 13% (0.6% to 37%) for acne, and 42% (9% to 79%) for neutropenia.

On the basis of the results of this meta-analysis, the authors concluded that islet transplant improved insulin independence and reduced hypoglycemia episode in some recipients. However, no information was available in terms of improvement in secondary complications, long-term survival, and quality of life. Nor was information was available regarding the comparative efficacy of islet transplantation versus intensive insulin therapy.

The Blue Cross Blue Shield report[21] included 12 primary studies from five centres (total 47 patients) and two studies on adverse events only, which were published before October 2003. Registry data, conference abstracts, and presentations by investigators from key research centres were also included as supplementary sources because of the scarcity of published articles. The authors did not formally assess the methodological quality of the included studies but noted several limitations of the published data, including small patient numbers, few transplant centres, short duration of follow-up, and lack of standardized methods of reporting outcomes. They also found that data were lacking on quality of life outcomes.

This report found that infrequent but serious adverse events (e.g., portal vein thrombosis or hemorrhage) occurred in patients who received islet transplantation, but it is not possible from present data to estimate their frequency. Recent modifications of the procedure reportedly minimized risks of these adverse events. No procedure-related deaths were reported among islet transplantation recipients. No information was available for the long-term consequence of immunosuppressive regimen.

In this report, no data were available for clinical outcomes with follow-up longer than one year. Only one Edmonton study reported on long-term diabetic complications. This report also found that it was premature to compare the effects of islet transplantation with the effects of whole organ pancreas transplantation.

The Ontario report[72] was published in 2003 and their conclusions were similar to those of the 2003 AHFMR report.

CLINICAL GUIDELINES

According to the 2008 Canadian Diabetes Association Clinical Practice Guidelines for the Prevention and Management of Diabetes in Canada,[2] "*islet transplant can result in transient insulin independence and can reliably stabilize blood*

glucose concentrations in people with glycemic liability." On the basis of the results from the Edmonton 5-year follow-up study,[47] the Guidelines recommended that islet transplant may be considered for individuals with type 1 diabetes and preserved renal function, but with persistent metabolic instability characterized by severe glycemic liability and/or severe hypoglycemia unawareness despite best efforts to optimize glycemic control. For each individual the risk of chronic immnuosuppression must be carefully weighed against the potential benefits of islet transplant.

The 2006 American Diabetes Association Guidelines[22] states that "*pancreatic islet transplantation holds significant potential advantages over whole gland transplants. Recent strides have been made in improving the success rates of this procedure. However, at this time, islet transplantation is a rapidly evolving technology that also requires systemic immunosuppression and should be performed only within the setting of controlled research studies.*"

According to the 2008 National Institute for Health and Clinical Excellence (NICE) Guidelines,[73] the evidence on allogeneic pancreatic islet cell transplantation for type 1 diabetes mellitus shows short-term efficacy with some evidence of long-term efficacy. The evidence on safety shows that serious complications may occur as a result of the procedure. The long-term immunosuppression required is also associated with a risk of adverse events. In units with established experience in allogeneic pancreatic islet cell transplantation, the procedure may be used with normal arrangements for clinical governance. Patient selection for this procedure should involve a multidisciplinary team. Selection criteria should take into account that the procedure is particularly indicated for patients with hypoglycemia unawareness and/or those already on immunosuppressive therapy because of renal transplantation. It should be noted that these guidelines did not specifically address ITA.

DISCUSSION

Methodology quality

The majority of the included primary studies are case series studies that are prone to all types of biases due to the absence of a control group. Case series studies are considered to be the weakest study design for testing the association between intervention and outcome.

However, case series studies are the only source of available evidence on the effects of ITA at this time. For outcome measures such as insulin independence, well-conducted case series study can still provide valid information because this outcome would not occur without the intervention (by definition, all patients with type 1 diabetes are insulin dependent).

Results from the methodological quality assessment of the 11 key case series studies indicated that, although the overall reporting of these studies was acceptable, only three studies sampled patients consecutively. Furthermore, small sample size (less than 20 in the majority of the studies), short follow-up period (usually up to one year), and lack of standardized outcome reporting significantly impact the interpretation of the studies' results.

Safety and efficacy of ITA

Is ITA a safe procedure for type 1 diabetic patients in the short term and longer-term in relation to procedure- and immunosuppression-related adverse events?

ITA has appeared to be relatively safe in terms of short-term (less than one year) procedure-related complications. In all included studies, no death has occurred that directly related to the ITA procedure. Intra-peritoneal bleeding, sometimes requiring blood transfusion or laparotomy, occurred in up to 14% of the procedures and in up to 25% of the patients. Portal vein thrombosis occurred in 6% to 17% of the patients. The patients with these complications were treated successfully and these adverse events decreased with prophylaxic measures. Only one patient was withdrawn from the study because of portal vein thrombosis.[54]

It should be noted that the relative risk of an acute bleeding or portal vein thrombosis after repeated islet infusions must be carefully balanced with the benefit sustained by further improvement in glycemic control. Avoidance of bleeding or portal thrombosis is critical to the safety of the islet transplant procedure, but measures used for prophylaxis against thrombosis may potentially exacerbate the risk of bleeding.[58]

Elevation of liver enzymes following islet transplantation appeared to be a common finding and occurred in up to 100% of the patients. However, this is a self-limited phenomenon that usually returned to normal range within one month without clinical consequence. Four of the 11 key studies reported hepatic steatosis (fatty liver) detected by magnetic resonance imaging or ultrasound in 8% to 33% of ITA recipients, but the clinical significance of this phenomenon remains unknown.

A variety of immunosuppression-related complications (most of them sirolimus-related), such as mouth ulcers, anemia, diarrhea, and edema are sometimes poorly tolerated or life threatening and have led to immunosuppression withdrawal and graft loss in some cases. Both the international trial[46] and the Edmonton study[47] found high frequency (89% to 92%) of mouth ulcers, which occasionally led to withdrawal of the immunosuppressive regimen.

A statistically significant decline in renal function was observed in up to 50% of the patients following the immunosuppressive treatment with the

combination of sirolimus and tacrolimus. The clinical significance of this small decline in renal function is not clear (Dr. Senior, personal communication, June 2008); however, this phenomena raised great clinical concerns as the treatment with sirolimus was originally thought to be less nephrotoxic.

In seven of the 11 key studies, the original immunosuppressive regimen had to be switched to alternative treatments due to its side effects. In the Edmonton study and the international multicentre study, the original sirolimus and tacrolimus based immunosuppressive regimen had to be changed in 23% and 25% of patients, respectively. Furthermore, although some rare immunosuppression-related complications, such as cancer, are not yet reported in the included studies, the overall small sample size and short period of follow-up period in most of the studies preclude a conclusion in this regard.

Is ITA effective in achieving insulin independence, improving glycemic control, and reducing hypoglycemia episodes during longer-term (one year or longer) follow-up?

Results from the included studies suggested that ITA is effective in achieving insulin independence with improved glycemic control over a short period of time (one year or less). Reported one-year insulin independence rates in those studies ranged from 30% to 69%. In the international multicentre trial,[46] an average of 44% of patients achieved insulin independence at one year; however the rates of insulin independence varied considerably (ranging from 22% to 67%) among the nine participating clinical centres depending on their previous experience.

Only a few studies reported results with follow-up periods longer than one year. These studies noted that islet function appeared to deteriorate over time. In the international multicentre study,[46] a progressive loss of full islet function was observed in most patients who became insulin independent initially but continued to have persistent C-peptide secretion. Only five of the 16 patients who achieved insulin independence at one year remained insulin free at 2 years. In the Edmonton study of 65 patients,[47] of the four patients who were available for follow-up at 5 years, only one patient remained insulin free. The reasons for the loss of islet grafts over time remain unclear. The investigators proposed that recurrent autoimmunity might play a role. Most immunosuppressive drugs, including tacrolimus and sirolimus, are known to impair islet function, particularly in the portal-hepatic site, and therefore may enhance diabetogenic toxic effects.

All studies reported improved glycemic control indicated by decreased HbA1c levels and reduced frequency and severity of hypoglycemia episodes following ITA in patients who achieved insulin independence as well as in patients with partial islet graft function. These results are encouraging as improved glycemic control and reduced hypoglycemia are very important to this group of patients. However, caution is required when interpreting these results given the nature of the case series design.

Is ITA effective in improving quality of life and secondary complications of diabetes?

Research evidence on the health-related quality of life following ITA is very limited. Findings from two studies indicated that fear of hypoglycemia was reduced following ITA. However, results regarding the impact of ITA on overall health-related quality of life are inconsistent. While one study with 10 patients[64] found improvement on the generic measures of health-related quality of life one year post-transplant, the other study of 99 patients with longer follow-up (up to 3 years) did not find any significant changes on the overall health-related quality of life measures.

ITA recipients may somewhat differ from whole organ pancreas transplantation recipients in that they often have not yet developed the advanced complications of diabetes.[50] It is of particular interest whether ITA can preserve this high baseline function in ITA recipients by restoring physiological insulin secretion and halting the progression of diabetic retinopathy and neuropathy.

Two studies[50,66] focused on the effects of ITA on the secondary complications of diabetes, including retinopathy and neuropathy. One study[50] demonstrated that all ITA recipients had stabilization of their diabetic retinopathy and that 50% of patients exhibited stabilization or even improvement of their diabetic neuropathy during a one-year follow-up. The other study[66] examined ITA recipients' retina blood flow using colour Doppler imaging and found that, at one year post-transplant, there was a statistically significant increase in the blood flow velocities of patients' central retinal artery and vein, which may reflect an increase of retinal blood flow (i.e., improvement in retinal microcirculation).

The lengths of follow-up in these studies are relatively short for measuring changes in secondary complications. The US Biologic Response Modifiers Advisory Committee suggested that, for islet transplantation, reasonable follow-up would be one year for identification of acute complications; 2 to 3 years for measuring immunosuppressive side effects, and 5 to 10 years for detecting long-term outcomes such as retinopathy and vascular function.[44] Thus, detecting the effect of islet transplantation on secondary complications of diabetes requires further study.

Is ITA comparable to intensive insulin therapy or pancreas transplantation in terms of safety and efficacy?

Only one retrospective study[23] attempted to compare islet transplantation with whole organ pancreas transplantation. This study used the data from a clinical centre in the United States and found that both whole organ pancreas transplantation and islet transplantation proved highly successful at establishing insulin independence in type 1 diabetic patients. Patients who received pancreas transplantation experienced longer lengths of hospital stay, more readmissions, and more post-operative complications, but they demonstrated a more durable state of normoglycemia with greater insulin reserves. In contrast, islet transplantation was associated with less procedure-related morbidity

and shorter hospital stays, but achieving insulin independence proved to be more expensive than whole organ pancreas transplantation mainly because of the requirement of multiple donors for sufficient islet cells. It should be noted that the higher cost of islet transplantation might reflect high cost organ procurement, which is not relevant in Canada (Dr. Senior, personal communication, June 2008).

The patients included in the two treatment groups were considerably different as the majority of the pancreas transplantation recipients had end-stage kidney disease requiring dialysis treatment. All pancreas transplantations were performed either in combination with or after kidney transplantation, whereas islet transplantations were performed either as ITA or after kidney transplantation, and the efficacy outcomes were not reported separately for ITA.

Only one study[57] compared ITA (21 patients) with intensive medical therapy (44 patients) using a partial crossover study design. This study found no statistically significant differences in glycemic control and in decline of renal function between the two groups. The patients included in this study had diabetic complications such as mild nephropathy or retinopathy but no recurrent severe hypoglycemia episode or hypoglycemia unawareness, which differed from the patients included in the 11 key studies.

The current standard of care for type 1 diabetes includes intensive insulin therapy, diet, and physical exercise. Whole organ pancreas transplantation in combination with kidney transplantation is an accepted treatment option for patients with end-stage kidney diseases. In the Edmonton protocol, eligible candidates for ITA are those patients with brittle diabetes, severe hypoglycemia or hypoglycemia unawareness, or patients who failed insulin therapy but had not yet developed end-stage kidney disease. ITA should be compared with pancreas transplantation alone (PTA) in a similar group of patients, i.e., non-uremic patients, because beta cell replacement with or without kidney transplantation act differently (Dr. Sutherland, personal communication, July 2008).

In conclusion, no primary research studies compared ITA with intensive insulin therapy or whole organ pancreas transplantation alone in non-uremic patients with severe hypoglycemia or hypoglycemia unawareness. The question remains unanswerable based on the available evidence.

Clinical issues

Patient eligibility

Most clinical trials selected patients based on the criteria used in the Edmonton protocol; that is, patients who are 18 to 65 years old, have had type 1 diabetes for more than 5 years, have undetectable C-peptide, and have severe hypoglycemia episodes or hypoglycemia unawareness with adequate renal reserve.

Only a small portion of type 1 patients might be eligible for ITA. In the international multicentre trial,[46] of approximately 2000 prospective patients screened for eligibility, only 149 (7%) fulfilled the initial stringent screening criteria and were referred to the sites. The risks associated with ITA indicate that the procedure in its current format is not suitable for all patients with type 1 diabetes.[74] Furthermore, if whole organ transplantation is required in the future, the chance of rejection is higher in this group of patients.

Longer term efficacy

Most included studies demonstrated short-term (one year or less) clinical efficacy of ITA; however, islet function deteriorated over longer periods of follow-up. The possible mechanisms for the destruction of the transplanted islets over time may include chronic allograft rejection, undiagnosed acute rejection, local islet toxicity from immunosuppressive drugs, recurrent autoimmunity, or failure of islet generation over time as a result of the antiproliferative properties of sirolimus.[16,75]

The role of the isolated islets themselves, their qualitative characteristics following isolation, purification, and transplantation, and the impact of the implant site and of the transplantation procedure may also contribute to low islet graft survival. These factors can cause a specific inflammatory responses that can, in turn, exacerbate both the autoimmune and alloimmune response in the patient.[16] Both immunologic as well as non-immunologic factors need careful consideration.[16]

Immunosuppression-related safety

Immunosuppressive medication sirolimus and tacrolimus have near-ubiquitous targets of distribution and, as a result, lead to a number of side effects including mouth ulceration, peripheral edema, a high rate of ovarian cysts in female patients, increase in proteinuria in some patients with underlying preexisting diabetic renal damage, hypertension, and hypercholesterolemia.[75]

Decline in renal function in some patients following ITA is an important observation. The cause the decline in renal function remains unclear. Effects of the immunosuppressive drugs (such as sirolimus and tacrolimus) on the kidneys or the progression of pre-exiting diabetic nephropathy may account for these changes. However, in this heterogeneous and complex population it is difficult to discriminate between the nephrotoxicity of the immunosuppressants and an acceleration of the pre-exiting underlying diabetic nephropathy or each of their relative contributions.[61]

The original Edmonton protocol with sirolimus and tacrolimus is under continuous modification because of their side effects. A recent study[76] compared the use of sirolimus with the use of sirolimus plus tacrolimus in 10 non-uremic type 1 diabetic patients. This study found that use of sirolimus

alone was not sufficient to suppress rejection after islet transplantation but was associated with increased risk of proteinuria.

The studies' results indicate the need for developing less toxic immunosuppressive drugs and highlight the importance that renal status be carefully assessed prior to transplant and monitored afterward.

Defining success of islet transplantation

The expectation and definition of success of islet transplantation still remain undefined and controversial.

Assessment of islet function in vivo is difficult because of the lack of direct measures to determine the viability of the islet cells. Due to the inability to directly measure islet cellular mass, patients who received pancreas and islet transplant are judged by their need for exogenous insulin, their glucose control, the frequency of hypoglycemia, and their endogenous insulin production (mostly determined by measuring circulating C-peptide concentrations).[38] Success after islet transplantation can thus be defined in terms of insulin independence, C-peptide secretion, or more stable glycemic control.[77]

The US FDA Biological Response Modifier Advisory Committee proposed a consensus definition of successful islet transplantation: restoration of sustained euglycemia with no or a reduced exogenous insulin requirement.[44] The 2008 Canadian Diabetes Association Clinical Guideline[2] recommended the following targets for glycemic control for type 1 diabetes: HbA1c levels ≤7.0%, fasting plasma glucose levels between 4.0 and 7.0 mmol/L, and 2-hour postprandial plasma glucose levels between 5.0 and 10.0 mmol/L. The international multicentre trial,[46] with a follow-up of 24 months, demonstrated that the mean HbA1c level were under 6.0% for patients who were insulin free and under 7.0% in patients with partial graft function; suggesting that the US FDA's definition of successful islet transplantation was met in this study.

The benefit of persistent islet function in the absence of insulin independence should not be entirely discounted.[75] Even if patients resume insulin therapy after islet transplantation, the required insulin doses are usually much lower than pre-transplant. Effective prevention of recurrent hypoglycemia or severe liability combined with correction in glycated hemoglobin to a level far superior to that readily achievable with intensive insulin therapy, is seen as a substantial benefit in this population with severe hypoglycemia and unstable glycemic control[75] It remains to be determined whether stable improvement in glycemic control from a partially functional islet transplant can be justified against the real and potential risks of current, life-long immunosuppressive therapy[75]

Allocation of donor pancreas

When considering islet transplantation versus whole organ pancreas transplantation, an important issue is allocation of pancreases from deceased

donors for either pancreas or islet transplantation.[19] Pancreas transplantation has a higher success rate but it is associated with significant surgical morbidity. Islet transplantation has a low procedure-related morbidity but is less efficient because of the attrition of islet function during isolation and engraftment. This problem creates the need for more than one donor (two to four) to achieve a sufficient beta-cell mass in many patients, and limits the number of candidates that can benefit.[19] Two studies conducted in Minnesota[35,78] reported encouraging results of using a single donor to achieve insulin independence and adequate glycemic control during a one-year follow-up. A longer-term follow-up study is needed to determine the long-term efficacy of islet transplantation using islets from a single donor as well as to define the characteristics of quality pancreas donors.

The study that compared islet transplantation with whole organ pancreas transplantation[23] suggested that islet transplantation be considered as a complement to rather than a replacement of whole organ pancreas transplantation because the donors used for islet transplantation were those rejected for whole organ transplantation. However, performing islet transplantation using leftovers may not be appropriate, and pancreas allocation should be integrated with a common list of candidates for pancreas or islet transplantation (Dr. Sutherland, personal communication, July 2008).

Future research

- Development of more sensitive methods to predict and detect graft loss and elucidate its mechanisms to preserve islet mass over time.
- Development of quality of life tools specific for islet transplantation patients so that improvements can be recorded in a quantitative manner.
- Prospective studies that compare the clinical results in patients with or without a history of renal dysfunction through a careful examination prior to islet transplant.
- Development of less kidney toxic immunosuppressive therapy.
- Improvement of safety and tolerability of the procedure and immunosuppression.
- Studies with longer follow-up periods ($>$ 5 years).
- Larger studies using single donors and standardized immunosuppressive regimen.
- Careful assessment of islet transplant recipients and their clinical outcomes to identify their unique issues and ongoing assessment of risk benefit ratio.
- Studies with longer follow-up to examine the impact of ITA on secondary complications of diabetes.

CONCLUSION

Since the first published study of the Edmonton protocol in 2000, interest in ITA procedure has been regenerated worldwide, and a substantial number of research studies have been undertaken. This report only included efficacy studies with a follow-up one year or longer.

Most studies applied the patient eligibility criteria used in the 2000 Edmonton protocol study: age 18 to 65 years, non-uremic type 1 diabetes for more than 5 years, recurrent severe hypoglycemia episodes and hypoglycemia unawareness, consistent negative C-peptide secretion, and no previous kidney transplant.

The original Edmonton protocol continues to undergo modifications, which includes new methods for donor pancreas preservation, islet culture prior to transplantation, using islets prepared from a single donor rather than from multiple donor organs, change of sirolimus and tacrolimus-based immunosuppressive regimens to other drugs such as mycophenolate mofetil.

In terms of safety, procedure-related complications, such as intraperitoneal bleeding and portal vein thrombosis, have been treated successfully. The risks of these complications were reduced as clinical experience increased and with the use of prophylaxis measures. The frequency of a variety of immunosuppression-related complications continues to be of greater clinical concern. Particularly, decline in renal function following the use of sirolimus and tacrolimus was observed in some patients. This sometimes led to discontinuation or change of the original immunosuppressive regimen. In most studies, no disease related to cytomegalovirus or Epstein-Barr virus, or post-transplant lymphoproliferative disease was observed after islet transplantation.

Limited evidence from the 11 case series studies with a total of 208 patients suggested that transplantation of adequate islet cells (usually from two to three pancreas donors) could restore insulin independence with adequate glycemic control in 30% to 69% (44% in the international multicentre trial) of the patients in the short term (one year or less). However, islet function appeared to deteriorate over time. In the international multicentre trial, only 14% of the patients remained insulin free at 2 years. The Edmonton 5-year follow-up study reported that less than 10% of the patients remained insulin free at 5 years, while 82% of patients maintained graft function measured by C-peptide secretion at 5 years. Partial islet function with reduced insulin requirement could provide protection from severe hypoglycemia and improve glycemic control. These results suggest that ITA may be effective in a small group of highly selective patients for whom the benefits of stable glycemia and freedom from hypoglycemia outweigh the potential risks of islet transplantation.

Results from two studies with a total of 109 patients demonstrated a reduction in fear of hypoglycemia, but not consistent in terms of overall health-related

quality of life measures. Quality of life tools need to be developed that are specific to ITA patients.

Preliminary results from two studies with a total of 22 patients showed an improvement in diabetic retinopathy and neuropathy following ITA; however, these studies, due to their weak design, are subject to biases and hence preclude any firm conclusion about outcomes.

There is currently no information available on the comparison of ITA with intensive insulin therapy in patients with severe hypoglycemia or hypoglycemia unawareness. No study directly compared ITA with pancreas transplantation alone (PTA) in non-uremic patients. Therefore, it is premature at this time to formulate conclusions about the superiority of one intervention over another.

How to define the success of ITA remains controversial. Insulin independence may not be an appropriate primary outcome. ITA should be aimed at reducing the frequency and severity of hypoglycemia to improve patients' quality of life, and improving glycemic control to prevent secondary complications of diabetes with lower doses of insulin therapy. The US FDA Biological Response Modifier Advisory Committee suggested a consensus definition of successful islet transplantation: restoration of sustained euglycemia with no or a reduced exogenous insulin requirement.

On the basis of the evidence presented in this report, ITA is an alternative therapeutic option for a small group of highly selective patients (i.e., non-uremic type 1 diabetic patients with severe hypoglycemia and uncontrolled diabetes). Current clinical research demonstrated encouraging short-term efficacy results. ITA continues to evolve and it is still premature to consider it as 'standard of care' for this group of patients.

The procedure currently faces several major obstacles, including the lack of a readily available source of human islets, the need for chronic immunosuppressive therapy, and the loss of insulin independence over time. In order to consider islet transplantation as a longer term (more than one year) option, future research is needed in exploring more sensitive methods to detect graft loss and elucidate its mechanisms to preserve islet mass over time, in developing less toxic immunosuppressive regimens, and in finding ways to reduce the number of islets required to reverse diabetes.

Alberta is in a unique position worldwide to continue to lead the field of islet transplantation. The lessons learned from in islet transplantation will be critical for future cell based therapies (e.g., replacement of engineered beta cells or stem cell therapy) for type 1 diabetes.

APPENDIX A: METHODOLOGY

Search strategy

A literature search was conducted by the AHFMR Research Librarian in November 2005 and was updated by the IHE Research Librarian in May 2008 to retrieve articles published between November 2002 and May 2008. The searches were further limited to English language articles and human studies where possible. Reference lists of relevant articles were also browsed to find more studies. The search strategy was created and carried out prior to the study selection process.

Medical Subject Headings (MeSH) terms relevant to this topic are: Islets of langerhans transplantation; Diabetes mellitus; Diabetes mellitus, Type 1

Table A.1: Search strategy

Database	Edition or date searched	Search Terms ††
Core Databases		
Cochrane Library Licenced Resource (Wiley Interface	May 7, 2008 Issue 2, 2008	(((islet* NEXT of NEXT langerhans) NEAR transplant*) OR (islets NEAR transplant*)) AND diabet*
PubMed www.pubmed.org	May 7, 2008	(islets of langerhans transplantation OR islet cell transplant* OR islets transplant* OR islet transplant*) AND (diabetes OR diabetic) AND Humans[Mesh]
CRD Databases (DARE, HTA & NHS EED) www.york.ac.uk/inst/crd/crddatabases.htm	May 7, 2008	Islet* AND transplant* AND diabet*
EMBASE Licensed Resource (OVID Interface)	May 7, 2008 (to 2008 Week 18)	(islet$ adj2 transplant$).mp. and diabet$.mp
Web of Science SCI-EXPANDED, SSCI Licensed Resource (ISI Interface)	May 7, 2008	TS=(((islet* SAME transplant*) AND diabet*) NOT (rat OR rats OR mice OR mouse OR dog* OR monkey)) Language=English
CINAHL Licensed Resource (EBSCO Interface)	May 7, 2008	1 MH "Islets of Langerhans" 2 transplant* 3 islet* cell* transplant* 4 islet* transplant* 5 (S1 and S2) or S3 or S4 Limit to English
Biosis Previews Licensed Resource (ISI Interface)	May 7, 2008	TS=((((islet* SAME transplant*) AND diabetes) NOT (rat OR mice OR dog*))) Language=English;

Table A.1: Search strategy (continued)

Database	Edition or date searched	Search Terms ††
Library Catalogues		
NEOS Library Catalogue www.library.ualberta.ca/catalogue	May 7, 2008	Islet$ AND transplant$
Guidelines		
US National Guideline Clearinghouse www.guideline.gov/	May 7, 2008	Islet* AND transplant*
Clinical Trials		
US Clinical Trials.gov www.clinicaltrials.gov	May 7, 2008	(islets of langerhans transplantation OR islet cell transplant* OR islets transplant* OR islet transplant*) AND (diabetes OR diabet*)
UK National Research Register www.nrr.nhs.uk/search.htm	July 24, 2007 (no longer avail May 2008)	(((islet* NEXT of NEXT langerhans) NEAR transplant*) OR (islets NEAR transplant*)) AND diabet*
Regulatory and Licensing Sites		
Alberta Health and Wellness www.health.gov.ab.ca	May 7, 2008	Islet transplant
Health Canada www.hc-sc.gc.ca	May 7, 2008	Islet* AND transplant*
US Food and Drug Administration www.fda.gov	May 7, 2008	Islet* transplant*
US Medicare Coverage Database www.cms.hhs.gov/mcd/search.asp?	May 7, 2008	Islet* transplant* (national coverage and local coverage - all words in title)
Aetna Clinical Policy Bulletins (used google.ca)	May 7, 2008	Islet transplantation site:aetna.com
BlueCross Blue Shield www.bcbs.com	May 7, 2008	Islet* transplant*
HTA Websites		
AETMIS www.aetmis.gouv.qc.ca/site/home.phtml	May 7, 2008	Islet; islets
CADTH www.cadth.ca/index.php/en/hta/reports-publications/search	May 7, 2008	Islet; islets

Table A.1: Search strategy (continued)

Database	Edition or date searched	Search Terms ††
HTA Websites (continued)		
ICES www.ices.on.ca	May 7, 2008	Islet; islets
Health Technology Assessment Unit At McGill www.mcgill.ca/tau/publications/	May 7, 2008	Browsed 2002—2008 Reports and Work in Progress
Medical Advisory Secretariat www.health.gov.on.ca/ english/providers/program/ohtac/tech/techlist_mn.html	May 7, 2008	Browsed list of reviews
ECRI www.ecri.org	May 7, 2008	Islet* AND transplant*
NICE (UK) www.nice.org.uk/page.aspx?o=ourguidance	May 7, 2008	Islet; islets
NZHTA http://nzhta.chmeds.ac.nz	May 7, 2008	Browsed publications list
Search Engine		
Google www.google.ca	May 7, 2008	Islet transplantation (first 50 results)

Note:

†† "*" and "$" are truncation characters that retrieve all possible suffix variations of the root word, e.g., surg* retrieves surgery, surgical, surgeon, etc. Semi-colons separate searches that were entered separately.

Study selection

One assessor (BG) reviewed all abstracts identified from the literature search and retrieved full text articles that appeared to be relevant. Key primary studies were selected according to the following predetermined inclusion and exclusion criteria.

Inclusion criteria

Studies were included if they met all of the following criteria:

- Study designs: systematic reviews/HTA reports, randomized controlled trials, non-randomized controlled clinical trials, cohort studies, case control studies, or case series studies.
- Patient population: adults (18 years or older) who had type 1 diabetes for more than 5 years with a history of severe hypoglycemia episodes or hypoglycemia unawareness, but without end stage renal disease.

- Index intervention: pancreatic islet allotransplantation alone using the Edmonton protocol or modifications of the Edmonton protocol.
- Comparative intervention: whole organ pancreas transplantation or intensive insulin therapy.
- Outcome measures: at least one of the following: safety (mortality, procedure-related, or immunosuppression-related adverse events) and efficacy (insulin independence or insulin requirement, hypoglycemia episode, C-peptide secretion, HbA1c level, health-related quality of life, or secondary complications of diabetes such as retinopathy, nephropathy, cardiovascular disease, etc). The follow-up period for efficacy outcome should be at least one year after final transplantation.
- English language full text articles published from November 2002 to May 2008.

Exclusion criteria

Studies were excluded if they met any of the following criteria:

- Abstracts, commentaries, research news, letters, and notes.
- Animal studies.
- Study participants were patients with type 2 diabetes, type 1 diabetes with severe kidney disease, chronic pancreatitis, or pancreas tumors; or patients who received other organ transplantation (kidney or lung) previously.
- Studies that assessed procedures such as islet cell auto-transplantation, xenotransplantation (or xenogeneic transplantation), genetically altered islets, islets prepared from stem cells, fetal pancreatic islet transplantation, liver-islet transplantation, kidney-islet transplantation, lung-islet transplantation, pancreas transplantation, and liver transplantation as the primary intervention of interest.
- Studies only focused on technical aspects of islet cell isolation, purification, storage, or delivery without any clinical outcomes, or studies focused on comparing different protocols.

Data extraction

One assessor (BG) abstracted data from each of the primary studies according to a standardized data extraction form developed a priori. A second assessor (CH) fact-checked the evidence table to ensure accuracy and consistency of data extracted. When required information was not available or not clear from the included studies, authors of these studies were contacted for clarification.

Methodological quality assessment

On the basis of 30 quality criteria derived from a literature search, an 18-item quality assessment checklist for case series studies was developed through a Delphi study conducted with a panel of seven HTA researchers from

Canada, Australia, and Spain. This checklist addresses several important aspects of case series studies, including study objective, patient characteristics, intervention and co-intervention, outcome measures, statistical analysis, results and conclusion, and competing interest. Five criteria, including multicentre study design, consecutive patient recruitment, before-and-after outcome measurement, reporting length of follow-up, and reporting of loss to follow up, were considered to be mandatory items for studies assessed in this report. Due to the limitations of using numerical scores to rate the quality of case series studies, a simple nominal rating scale was used such that studies were scored as positive (yes) or negative (no) for each quality criterion (Appendix C).

Two assessors (BG, PC) independently assessed the methodological quality of the 11 case series studies using this checklist. Any disagreements that could not be solved by discussion were referred to a third assessor for mediation until consensus was reached. The two assessors discussed the checklist with respect to the interpretation of the questions prior to assessing the studies. Critical appraisal results for all included case series studies are presented in Appendix C.

Data synthesis

Information from each of the included studies was summarized qualitatively in this review. It was not possible to perform a meta-analysis because of the lack of a standardized definition for outcome measures, different ways of reporting the same type of outcomes, and variability in treatment protocols and immunosuppressive regimen. Characteristics of treatment protocols used in the included studies are presented in the evidence summary table but this review makes no attempt to compare the outcome of different protocols.

External review

External reviewers with clinical expertise in islet transplantation and/or health technology assessment methodologies evaluated the draft report and provided feedback. In selecting reviewers, the practice of the Institute of Health Economics is to choose experts who are well recognized and published in peer reviewed literature, and who can offer a provincial and/or national perspective with respect to the use of islet transplantation.

APPENDIX B: EXCLUDED STUDIES

Table B.1: Excluded primary study and reason for exclusion

Study	Reason for exclusion
Alejandro et al. Insulin independence following transplantation of cultured human islets in patients with type 1 diabetes. *Transplantation* 2003;76(4):S24	Abstract
Alejandro et al. Insulin independence in 13 patients following transplantation of cultured human islets. *Cell Transplantation* 2003;12(2).	Abstract
Alejandro et al. Insulin independence following transplantation of cultured human islets in patients with type 1 diabetes: The Miami experience. *American Journal of Transplantation* 2004;4:553.	Abstract
Alejandro et al. Update from the Collaborative Islet Transplant Registry. *Xenotransplantation* 2007;14(5).	Abstract
Al Riyami et al. Improvement in diabetic neuropathy following islet transplantation. *Xenotransplantation* 2007;14(5):473.	Abstract
Al-Sayed et al. Improved graft survival following islet transplantation using higher sirolimus levels. *Xenotransplantation* 2007;14(5).	Abstract
Ault. Edmonton's islet success tough to duplicate elsewhere. *Lancet* 2003;361:9374-2054.	News
Bansal-Pakala et al. HOKT3gamma Ala, Ala induces higher treg frequencies in islet transplant patients correlating with long-term graft survival. *Xenotransplantation* 2007;14(5):429-30.	Abstract
Barshes et al. Achievement of insulin independence via pancreatic islet transplantation using a remote isolation center: a first-year review. *Transplantation Procedures* 2004;36(4):1127-29.	Length of follow-up not reported
Battetazzati et al. Effect of rapamycin on the counterregulatory response to hypoglycemia in islet transplant recipients. *Diabetes* 2005;54(Suppl 1):A488.	Abstract
Berney et al. Results of islet transplant alone (ITA) and islet after kidney (IAK) transplantation in 24 patients with type 1 diabetes in a multicenter network. *American Journal of Transplantation* 2005;5:274.	Abstract
Bhargava et al. Prevalence of hepatic steatosis after islet transplantation and its relation to graft function. *Diabetes* 2004;53(5):1311-17.	Earlier report of the Edmonton series
Bucher et al. Islet of Langerhans transplantation for the treatment of type 1 diabetes. *Swiss Surgery* 2003;9(5):242-46.	Results on ITA not reported separately
Bucher et al. Morbidity associated with intraportal islet transplantation. *Transplantation Proceedings* 2004;36(4):1119-20.	Results on ITA not reported separately
Calafiore et al. Standard technical procedures for microencapsulation of human islets for graft into nonimmunosuppressed patients with type 1 diabetes mellitus. *Transplantation Proceedings* 2006;38(4):1156-57.	Focused on technical aspect

Table B.1: Excluded primary study and reason for exclusion (continued)

Study	Reason for exclusion
Calafiore et al. Microencapsulated pancreatic islet allografts into nonimmunosuppressed patients with type 1 diabetes: first two cases. *Diabetes Care* 2006;29(1):137-8.	Follow up less than one year
Eich et al. Visualization of early engraftment in clinical islet transplantation by positron-emission tomography. *New England Journal of Medicine* 2007;356(260:2754-55.	Case report
Faradji et al. C-peptide and glucose values in the peritransplant period after intraportal islet infusions in type 1 diabetes. *Transplantation Proceedings* 2005;37(8):3433-35.	Follow up less than one year
Faradji et al. Continuous glucose monitoring system for early detection of graft dysfunction in allogenic islet transplant recipients. *Transplantation Proceedings* 2006;38(10):3274-76.	Follow up less than one year
Faradji et al. Remarkable metabolic control and insulin independence after single donor allogeneic islet mransplantation in a patient with type 1 diabetes under alemtuzumab induction. *Diabetes* 2006;55(Suppl 1):A616-17.	Abstract
Fernandes et al. Transplants of beta cells alone without accompanying islet non-beta cells successfully reverse diabetes. *Diabetes* 2006;55:A23.	Abstract
Fiorina et al. Early improvement of retinal blood flow in type 1 diabetes after islet transplant alone. *Diabetes* 2005;54:A485.	Abstract
Fiorina et al. Early improvement of retinal blood flow in type 1 diabetes after islet transplant alone. *American Journal of Transplantation* 2005;5:355.	Abstract
Frank et al. Comparison of whole organ pancreas and isolated islet transplantation for Type 1 Diabetes. *American Journal of Transplantation* 2004;4:552-3.	Abstract
Fung et al. Comparison of islet cell transplantation and intensive medical therapy in the treatment of type 1 diabetes mellitus. *Diabetes* 2005;54:A85-6.	Abstract
Fung et al. Effect of glucagon-like peptide-1 (7-37) on beta-cell function after islet transplantation in type 1 diabetes. *Diabetes Research & Clinical Practice* 2006;74(2):189-93.	Follow-up less than one year
Garfinkel et al. Interim Report of the University of Chicago series with islet transplantation via the Edmonton protocol. *Xenotransplantation* 2007;15(4).	Abstract
Geiger et al. Evaluation of metabolic control using a continuous subcutaneous glucose monitoring system in patients with type 1 diabetes mellitus who achieved insulin independence after islet cell transplantation. *Cell Transplantation* 2005;15(2-3):77-84.	Focused on a glucose monitoring system
Gillard et al. Influence of beta-cell number in cultured implants on their short-term metabolic outcome after transplantation in type 1 diabetic patients. *Diabetes* 2003;52(Suppl 1).	Abstract

Table B.1: Excluded primary study and reason for exclusion (continued)

Study	Reason for exclusion
Gillard et al. Side-effects of immune therapy using a combination of ATG-MMF-tacrolimus for beta-cell transplantation in non-uremic type 1 diabetic patients. *Diabetes* 2005;54(Suppl 1):A87.	Abstract
Gillard et al. Comparison of sirolimus alone with sirolimus plus tacrolimus in type 1 diabetic recipients of cultured islet cell grafts. *Transplantation* 2008;85(2):256-63.	Focused on comparing two different protocols
Goss et al. Pancreatic islet transplantation: the radiographic approach. *Transplantation* 2003;76(1):199-203.	Focused on the technical aspects
Goto et al. Successful islet transplantation from a single pancreas harvested from a young, low-BMI, non-heart-beating cadaver. *Transplantation Proceedings* 2005;37(8):3430-32.	Case report
Hafiz et al. Immunosuppression and procedure-related complications in 26 patients with type 1 diabetes mellitus receiving allogeneic islet cell transplantation. *Transplantation* 2005;80(12):1718-28.	Same series reported in Froud et al. 200548
Hering et al. Successful single donor islet transplantation in type 1 diabetes. *Transplantation* 2003;76(4):S23.	Abstract
Hering et al. Long-term (> 4 yrs) insulin independence after single-donor islet transplantation in type diabetes with hOKT3g-1 (Ala-Ala), sirolimus, and tacrolimus therapy. *American Journal of Transplantation* 2005;5:275.	Abstract
Hering et al. Analysis of long-term islet allograft function in recipients with type 1 diabetes given depleting t-cell antibodies for induction immunosuppression. *Xenotransplantation* 2007;14(5).	Abstract
Hirsch et al. Insulin secretory reserve is impaired in islet recipients despite return to normoglycemia. *Xenotransplantation* 2007;14(5):473-4.	Abstract
Hirshberg et al. Benefits and risks of solitary islet transplantation for type 1 diabetes using steroid-sparing immunosuppression. *Diabetes Care* 2004;27(5):1250-1.	Letter
Hong-McAtee et al. Predictors of long-term (> 1 yr) insulin independence in type 1 diabetic islet allograft recipients. *Diabetes* 2005;54(Suppl 1):A488.	Abstract
Iwanaga et al. Living donor islet transplantation, the alternative approach to overcome the obstacles limiting transplant. *Annals of the New York Academy of Sciences* 2006;1079:335-9.	Case report
Kessler et al. Tacrolimus-associated optic neuropathy after pancreatic islet transplantation using a sirolimus/tacrolimus immunosuppressive regimen. *Transplantation* 2006;81(4):636-7.	Case report
Lobo et al. Development of anti-human leukocyte antigen class 1 antibodies following allogeneic islet cell transplantation. *Transplantation Proceedings* 2005;37(8):3438-40.	Case report
Lundgren et al. Islet transplantation in the Nordic Network: an update. *Acta Diabetologica* 2005;42(1):54-5.	Abstract

Table B.1: Excluded primary study and reason for exclusion (continued)

Study	Reason for exclusion
Gillard et al. Side-effects of immune therapy using a combination of ATG-MMF-tacrolimus for beta-cell transplantation in non-uremic type 1 diabetic patients. *Diabetes* 2005;54(Suppl 1):A87.	Abstract
Gillard et al. Comparison of sirolimus alone with sirolimus plus tacrolimus in type 1 diabetic recipients of cultured islet cell grafts. *Transplantation* 2008;85(2):256-63.	Focused on comparing two different protocols
Goss et al. Pancreatic islet transplantation: the radiographic approach. *Transplantation* 2003;76(1):199-203.	Focused on the technical aspects
Goto et al. Successful islet transplantation from a single pancreas harvested from a young, low-BMI, non-heart-beating cadaver. *Transplantation Proceedings* 2005;37(8):3430-32.	Case report
Hafiz et al. Immunosuppression and procedure-related complications in 26 patients with type 1 diabetes mellitus receiving allogeneic islet cell transplantation. *Transplantation* 2005;80(12):1718-28.	Same series reported in Froud et al. 200548
Hering et al. Successful single donor islet transplantation in type 1 diabetes. *Transplantation* 2003;76(4):S23.	Abstract
Hering et al. Long-term (> 4 yrs) insulin independence after single-donor islet transplantation in type diabetes with hOKT3g-1 (Ala-Ala), sirolimus, and tacrolimus therapy. *American Journal of Transplantation* 2005;5:275.	Abstract
Hering et al. Analysis of long-term islet allograft function in recipients with type 1 diabetes given depleting t-cell antibodies for induction immunosuppression. *Xenotransplantation* 2007;14(5).	Abstract
Hirsch et al. Insulin secretory reserve is impaired in islet recipients despite return to normoglycemia. *Xenotransplantation* 2007;14(5):473-4.	Abstract
Hirshberg et al. Benefits and risks of solitary islet transplantation for type 1 diabetes using steroid-sparing immunosuppression. *Diabetes Care* 2004;27(5):1250-1.	Letter
Hong-McAtee et al. Predictors of long-term (> 1 yr) insulin independence in type 1 diabetic islet allograft recipients. *Diabetes* 2005;54(Suppl 1):A488.	Abstract
Iwanaga et al. Living donor islet transplantation, the alternative approach to overcome the obstacles limiting transplant. *Annals of the New York Academy of Sciences* 2006;1079:335-9.	Case report
Kessler et al. Tacrolimus-associated optic neuropathy after pancreatic islet transplantation using a sirolimus/tacrolimus immunosuppressive regimen. *Transplantation* 2006;81(4):636-7.	Case report
Lobo et al. Development of anti-human leukocyte antigen class 1 antibodies following allogeneic islet cell transplantation. *Transplantation Proceedings* 2005;37(8):3438-40.	Case report
Lundgren et al. Islet transplantation in the Nordic Network: an update. *Acta Diabetologica* 2005;42(1):54-5.	Abstract

Table B.1: Excluded primary study and reason for exclusion (continued)

Study	Reason for exclusion
Maffi et al. Comparison of islet transplantation in two groups of patients: Islet after kidney and islet alone. *Cell Transplantation* 2003;12(2).	Abstract
Maffi et al. Kidney function after islet transplantation alone. *Diabetes* 2005;54(Suppl 1):A87.	Abstract
Maffi et al. Islet with kidney versus islet transplantation alone: Clinical experience in patients with type 1 diabetes. *American Journal of Transplantation* 2007;7:571-2.	Abstract
Maffi et al. Islet transplantation alone in type 1 diabetes: Single center experience. *American Journal of Transplantation* 2004;4:377.	Abstract
Maffi et al. Islet transplantation in type 1 diabetes: overall experience in a single center. *Xenotransplantation* 2007;14(5):429.	Abstract
Maleux et al. Feasibility, safety, and efficacy of percutaneous transhepatic injection of beta-cell grafts. *Journal of Vascular and Interventional Radiology* 2005;16(12):1693-7.	Follow-up less than one year
Markmann et al. Insulin independence following isolated islet transplantation and single islet infusions. *Annals of Surgery* 2003;237(6):741-9.	Follow-up period not clearly reported
Matsumoto & Tanaka. Pancreatic islet cell transplantation using non-heart-beating donors (NHBDs). *Journal of Hepatobiliary Pancreatic Surgery* 2005;12(3):227-30.	Follow-up less than one year
Matsumoto et al. Insulin independence of unstable diabetic patient after single living donor islet transplantation. *Transplantation Proceedings* 2005;37(8):3427-9.	Case report
Matsumoto et al. Successful islet transplantation from nonheartbeating donor pancreata using modified Ricordi islet isolation method. *Transplantation* 2006;82(4):460-5.	Case report
McDonald et al. Cross-sectional and prospective association between proinsulin secretion and graft function after clinical islet transplantation. *Transplantation* 2004;78(6):934-7.	Earlier report of the Edmonton series
Milliat-Guttard et al. Patients with type 1 diabetes: quality of life after islet of langerhans allotransplantation. *Xenotransplantation* 2007;14(5):474-5.	Abstract
Nano et al. Islet isolation for allotransplantation: variables associated with successful islet yield and graft function. *Diabetologia* 2005;48(5):906-12.	Follow-up less than one year
Noguchi et al. Evaluation of islet transplantation from non-heart beating donors. *American Journal of Transplantation* 2006;6(10):2476-82.	Follow-up less than one year
Okitsu et al. Kyoto islet isolation method: the optimized one for non-heart-beating donors with highly efficient islet retrieval. *Transplantation Proceedings* 2007;37(8):3391-2.	Abstract
Okitsu et al. Islet allografts from non-heart beating donors in Type 1 diabetic patients at Kyoto, Japan: Two year follow up. *Xenotransplantation* 2007;14(5).	Abstract

Table B.1: Excluded primary study and reason for exclusion (continued)

Study	Reason for exclusion
Owen et al. Percutaneous transhepatic pancreatic islet cell transplantation in type 1 diabetes mellitus: radiologic aspects. *Radiology* 2003;29(1):165-70.	Earlier report of the Edmonton series
Paty et al. Assessment of glycemic control after islet transplantation using the continuous glucose monitor in insulin-independent versus insulin-requiring type 1 diabetes subjects. *Diabetes Technology & Therapeutics* 2006;8(2):165-73.	Focused on a glucose monitor system
Poggioli et al. Quality of life after islet transplantation. *Diabetes* 2005;54(Suppl 1):A87.	Abstract
Poggioli et al. Quality of life after islet transplantation. *American Journal of Transplantation* 2005;6(2):371-8.	Data on ITA not reported separately
Rafael et al. Changes in liver enzymes after clinical islet transplantation. *Transplantation* 2003;76(9):1280-4.	Earlier report of the Edmonton series
Rickels et al. Islet cell hormonal responses to hypoglycemia after human islet transplantation for type 1 diabetes. *Diabetes* 2005;54(11):3205-11.	Follow-up less than one year
Rickels et al. Glycemic thresholds for activation of counterregulatory hormone and symptom responses in islet transplant recipients. *The Journal of Clinical Endocrinology and Metabolism* 2007;92(3):873-9.	Follow-up less than one year
Rickels et al. Insulin sensitivity, glucose effectiveness, and free fatty acid dynamics after human islet transplantation for type 1 diabetes. *The Journal of Clinical Endocrinology and Metabolism* 2007;91(6):2138-44.	Did not report on the clinical outcomes of interest
Ruder. Islet transplants: mixed results. *Diabetes Forecast* 2007;60(4):16.	News
Ryan & Shapiro. A patient with severe, recurrent hypoglycemia and glycemic lability who underwent islet transplantation. *Nature Clinical Practice. Endocrinology & Metabolism* 2006;2(6):349-53.	Case report
Ryan et al. Assessment of the severity of hypoglycemia and glycemic lability in type 1 diabetic subjects undergoing islet transplantation. *Diabetes* 2004;53(4):955-62.	Focused on using a new scoring system
Ryan et al. Beta-score: an assessment of beta-cell function after islet transplantation. *Diabetes Care* 2005;28(2):343-7.	Focused on a new scoring system
Sassa et al. A single transplantation of the islets can produce glycemic stability and reduction of basal insulin requirement. *Diabetes Research & Clinical Practice* 2006;73(3):235-40.	Follow-up less than one year
Senior et al. Magnetic resonance-defined perinephric edema after clinical islet transplantation: a benign finding associated with mild renal impairment. *Transplantation* 2004;78(6):945-8.	Earlier report of the Edmonton series
Senior et al. Proteinuria developing after clinical islet transplantation resolves with sirolimus withdrawal and increased tacrolimus dosing. *American Journal of Transplantation* 2005;5(9):2318-23.	Earlier report of the Edmonton series
Senior et al. Body composition improves following clinical islet transplantation. *Diabetes* 2006;55(Suppl 1).	Abstract

Table B.1: Excluded primary study and reason for exclusion (continued)

Study	Reason for exclusion
Shah et al. A case of pancreatic islet cell transplantation in a patient with situs ambiguous: Anatomical and radiological considerations. *Seminars in Interventional Radiology* 2007;24(1):43-6.	Case report
Shapiro et al. Edmonton's islet success has indeed been replicated elsewhere. *Lancet* 2003;362(9392):1242.	Letter
Street et al. Islet graft assessment in the Edmonton Protocol: implications for predicting long-term clinical outcome. *Diabetes* 2004;53(12):3107-14.	Earlier report of the Edmonton series
Tanne. New technique improves safety of islet cell transplantation. *British Medical Journal* 2005;331(7528):1290.	News

ITA: islet transplantation alone

APPENDIX C: QUALITY ASSESSMENT RESULTS

Quality assessment checklist

Study objective

1. Is the hypothesis/aim/objective of the study clearly stated in the abstract, introduction or methods section?

Study population

2. Are the characteristics of the participants included in the study described?

   (To be answered yes, patient number, age, gender, duration of diabetes, and renal function should be reported.)

3. Were the cases collected in more than one centre?

4. Are the eligibility criteria (inclusion and exclusion criteria) to enter the study explicit and appropriate?

   (To be answered yes, criteria such as age, duration of diabetes, severe hypoglycemia or hypoglycemia unawareness, non-uremic, no previous kidney transplantation should be included.)

5. Were participants recruited consecutively?

   (To be answered yes, a clear statement that the participants are recruited consecutively should be provided.)

6. Did participants enter the study at a similar point in the disease?

   (To be answered yes, all of the following criteria should be met: 1) all patients have diabetes ≥ 5 years; 2) ≥80 of patients have severe hypoglycemia or hypoglycemia unawareness; 3) ≥ 80% of patients have no kidney disease. The question should be answered "no" if 1) not all criteria above are not met; 2) there is no clear description of these characteristics; or 3) information is not available for one of these characteristics.)

Intervention and co-intervention

7. Was the intervention clearly described in the study?

   (To be answered yes, information regarding number of islet/per infusion, frequency of infusion, and immunosuppressive therapy should be provided.)

8. Were additional interventions (co-interventions) clearly reported in the study?

   (To be answered yes, co-interventions such as diet change, exercise, or insulin therapy should be reported.)

Outcome measures

9. Are the outcome measures clearly defined in the introduction or methodology section?

   (To be answered yes, outcome measures such as insulin independence or insulin requirement, C-peptide secretion, HbA1c levels, occurrence of hypoglycemia episodes, secondary complications, or quality of life measures should be defined in the introduction or method section.)

10. Were relevant outcomes appropriately measured with objective and/or subjective methods?

11. Were outcomes measured before and after intervention?

Statistical analysis

12. Were the statistical tests used to assess the relevant outcomes appropriate?

Results and conclusions

13. Was the length of follow-up reported?

14. Was the number lost to follow up reported?

15. Does the study provide estimates of the random variability in the data analysis of relevant outcomes?

    (To be answered yes, the study should report estimates of the random variability such as standard error, standard deviation, or confidence intervals for all relevant primary and secondary outcomes.)

16. Are adverse events reported?

17. Are the conclusions of the study supported by results?

Competing interest and source of support

18. Are both competing interest and source of support for the study reported?

    (To be answered yes, both competing interest and source of financial or other support received for the study should be reported; or the absence of any competing interest and source of support is acknowledged.)

Table C.1: Study quality assessment results

Study Characteristic	
Study objective	1. Is the hypothesis/aim/objective of the study clearly stated in the abstract, introduction or methods section?
Study population	2. Are the characteristics of the participants included in the study described?
	3. Were the cases collected in more than one centre?
	4. Are the eligibility criteria to entry the study explicit and appropriate?
	5. Were participants recruited consecutively?
	6. Did participants enter the study at a similar point in the disease?
Intervention and co-intervention	7. Was the intervention clearly described in the study?
	8. Were additional interventions (co-interventions) clearly reported in the study?
Outcome measures	9. Are the outcome measures clearly defined in the introduction or methodology section?
	10. Were relevant outcomes appropriately measured with objective and/or subjective methods?
	11. Were outcomes measured before and after intervention?
Statistical analysis	12. Were the statistical tests used to assess the relevant outcomes appropriate?
Results and conclusion	13. Was the length of follow-up reported?
	14. Was the number lost to follow up reported?
	15. Does the study provide estimates of the random variability in the data analysis of relevant outcomes?
	16. Are adverse events reported?
	17. Are the conclusions of the study supported by results?
Competing interest and source of support	18. Are both competing interest and source of support for the study reported?
Total number of "yes" responses	

+ = yes / - = no

	Shapiro et al.[46]	Ryan et al.[47]	Froud et al.[48]	Hering et al.[35]	Hering et al.[49]	Hirshberg et al.[27]
	+	+	+	+	+	+
	+	+	+	+	+	+
	+	-	-	-	-	-
	+	-	-	+	+	+
	-	+	-	+	-	-
	+	-	+	-	+	-
	+	+	+	+	+	+
	-	+	+	+	+	-
	+	+	+	+	+	+
	-	+	+	+	+	-
	+	+	+	+	+	+
	+	+	+	+	+	-
	+	+	+	+	+	+
	+	+	+	+	+	+
	+	+	+	+	+	-
	+	+	+	+	+	+
	+	+	+	+	+	+
	+	-	-	+	+	-
	15	14	14	16	16	10

Table C.1: Summary of primary studies (continued)

Study Characteristic	
Study objective	1. Is the hypothesis/aim/objective of the study clearly stated in the abstract, introduction or methods section?
Study population	2. Are the characteristics of the participants included in the study described?
	3. Were the cases collected in more than one centre?
	4. Are the eligibility criteria to entry the study explicit and appropriate?
	5. Were participants recruited consecutively?
	6. Did participants enter the study at a similar point in the disease?
Intervention and co-intervention	7. Was the intervention clearly described in the study?
	8. Were additional interventions (co-interventions) clearly reported in the study?
Outcome measures	9. Are the outcome measures clearly defined in the introduction or methodology section?
	10. Were relevant outcomes appropriately measured with objective and/or subjective methods?
	11. Were outcomes measured before and after intervention?
Statistical analysis	12. Were the statistical tests used to assess the relevant outcomes appropriate?
Results and conclusion	13. Was the length of follow-up reported?
	14. Was the number lost to follow up reported?
	15. Does the study provide estimates of the random variability in the data analysis of relevant outcomes?
	16. Are adverse events reported?
	17. Are the conclusions of the study supported by results?
Competing interest and source of support	18. Are both competing interest and source of support for the study reported?
Total number of "yes" responses	

+ = yes / - = no

	Lee et al.[50]	Maffi et al.[51]	Keymeulen et al.[52]	Badet et al.[53]	O' Connell et al.[54]
	+	+	+	+	+
	+	+	+	+	+
	-	-	-	+	-
	+	+	+	+	+
	-	-	+	-	-
	-	+	-	+	+
	+	+	+	-	+
	-	+	+	+	-
	+	+	+	+	+
	+	-	+	+	-
	+	+	+	+	+
	+	+	+	+	_
	+	+	+	+	+
	+	+	+	+	+
	-	+	-	+	-
	+	+	+	+	+
	+	+	+	+	+
	-	-	-	-	+
	12	14	14	15	12

APPENDIX D: SAFETY AND EFFICACY SUMMARY TABLE

Continuous variables are expressed in mean ± standard deviation unless otherwise indicated.

Table D.1: Summary of safety and efficacy results

Study	Patient	Intervention
Shapiro et al. 2006[46] International multicentre trial (9 centres, 6 in America, 3 in Europe)	**Total No.:** 36 **Age (yr):** 41 ± 2(SE) **Gender (M/F):** NA **Duration of DM (yr):** 27±2 (SE) **BMI (kg/m²):** 22 (SE < 1) **Hypoglycemia:** 35 (97%) pts (severe, recurrent) **Labile diabetes:** 20 (56%) pts (severe) **Baseline renal function:** 2/36 pts (6%) had micro- and 1/36 pts (3%) had microalbuminuria.	**Culture of islets:** no **No. of infusions:** 1: 11 pts (31%) 2: 9 pts (25%) 3: 16 pts (44%) **Total IE/kg:** 13,473 ± 923 (range 5,189 to 22,482) **Immunosuppressive regimen:** Edmonton protocol (DAC, SIR, TAC) **Follow-up:** median 41 (range 37 to 50) months after the first transplantation 1 yr: 36 pts 2 yrs: 35 pts 3 yrs: 21 pts

* $P < 0.001$ for the comparison between the insulin-independence group and the partial-function group, and $P < 0.001$ for the comparison between baseline and each follow-up time point in both groups.

** $P = 0.17$ for the comparison between the insulin-independence group and the partial-function group, and $P < 0.001$ for the comparison between baseline and each follow-up time point in both groups.

*** Data extracted from Figure 2 in the study. $P < 0.001$ for the comparison between the insulin-independence group and the partial-function group, and $P < 0.001$ for the comparison between baseline and each follow-up time point, except 12 months in both groups.

	Efficacy	Adverse events
	Insulin independence: Any time: 21/36 pts (58%) 1 yr: 16 /36 pts (44%) (5 pts with 1 infusion, 6 pts with 2 infusions, 5 pts with 3 infusions) 2 yrs: 5/36 (14%) pts Partial graft function (C-peptide ≥ 0.3 ng/ml but require insulin): Any time: 24/36 pts (67%) 1 yr: 10/36 pts (28%) Complete graft loss: 10/36 pts (28%) **Insulin requirement:** reduced in insulin independent or partial graft function pts over 2 yrs* **Hypoglycemia:** full protection in insulin independent group **C-peptide secretion:** detectable (≥ 0.3 ng/ml) in 70% of pts at 2 yrs** **HbA1c (%):** reduced in insulin independent (under 6.0) or partial graft function (under 7.0) pts over 2 yrs*** **Health quality of life:** NA **Secondary complications of DM:** NA	**Procedure-related:** Total No. of serious events: 38 *Death:* 0 *Intra-peritoneal bleeding:* 7/77 (9%) procedures, 4 requiring blood transfusion, 1 requiring laparotomy *PVT:* partial branch-vein occlusion in 2/36 pts (6%) *Liver abnormality:* mild hepatic steatosis on MRI in 4/13 pts (31%) at 2 yrs **Immunosuppression-related:** *Renal function:* sCr increased 0.007 mg/dl/mo (P= 0.001); CrCl decreased 0.45 ml/min/1.73 m^2/mo (P=0.06); 13/36 pts (36%) developed microalbuminuria during follow-up. *Change in IS regimen:* 9/36 pts (25%) switched to a non-SIR-based alternative immunosuppressive regimen because of side effects. *IS discontinuation:* 2 pts (1 due to headache, 1 due to mouth ulcer and diarrhea) *Other:* mouth ulcers (92%), anemia (81%), leucopenia (75%), diarrhea (64%), headache (56%), neutropenia (53%), nausea (50%), vomiting (42%), acne (39%), and fatigue (39%), no CMV infection, no PTLD, no cancer

Table D.1: Summary of safety and efficacy results (continued)

Study	Patient	Intervention
Ryan et al. 2005[47] University of Alberta, Edmonton, Canada Single centre	**Total No.:** 65 **Age (yr):** 42.9 ± 1.2 **Gender (M/F):** 28/37 **BMI (kg/m²):** NA **Duration of DM (yr):** 27.1 ± 1.3 **Hypoglycemia:** 52 pts (80%) (pragmatic*) **Labile diabetes#:** 39 pts (60%) **Baseline renal function:** microalbuminuria in 35% with macroalbuminuria (> 0.2g/d) in 25% of pts	**Culture of islets:** yes (69% of the procedures) **No. of infusions:** 1: 13 pts 2: 41 pts 3: 11 pts At 1st infusion, islets from 2 donors in 8 procedures; at both 2nd and 3rd infusions, islets from 2 donors in 2 procedures **Total IE/kg:** 11,910 ± 469 (for 44 pts who achieved insulin independence) **Immunosuppressive regimen:** DAC, SIR, TAC 10 pts used infliximab, 9 pts used a lymphocyte depletion protocol (Campath-1H, ultra low-dose TAC and higher-dose SIR) **Follow-up:** median 35.5 (range 4.1 to 67.8) months for 47 pts who completed procedure

Continuous variables are expressed in mean ± SE unless otherwise indicated.

* Problematic hypoglycemia was defined as frequent recurrent episodes of hypoglycemia usually associated with hypoglycemia unawareness and more recently quantified with a hypoglycemic score (HYPO score) of ≥ 1,047.

Labile diabetes was defined as frequent wide swings in blood glucose that interfere with the patient's lifestyle and was characterized by a MAGE > 11.1mmol/l and more frequently by a liability index of ≥ 433mmol/l² · h⁻¹ · week⁻¹

	Efficacy	Adverse events
	Insulin independence: One month: 44/65 pts (68%) 5 yrs: 7.5% **Insulin requirement (U/kg/d):** decreased in pts on insulin but had persist C-peptide secretion: 0.34 ± 0.04 post- vs. 0.66 ± 0.03 pre-transplant ($P < 0.001$); increased in pts who lost islet function: 0.80± 0.08 post- vs. 0.69 ± 0.08 pre-transplant ($P = 0.03$) **Hypoglycemia:** HYPO scores significantly improved for up to 4 yrs, some hypoglycemia episodes occurred with the use of insulin. **C-peptide secretion (nmol/l):** lower in pts on insulin than those off insulin both basally (0.49 ± 0.05 vs. 0.86 ± 0.05, $P < 0.001$) and post-stimulation (0.93 ± 0.08 vs. 1.62 ± 0.07, $P<0.001$) (time of measurement not reported.) **HbA1c (%):** median 6.4 (IQR 6.1 to 6.7) in pts off insulin vs. 6.7 (IQR 5.9 to 7.5) in pts who resumed insulin but C-peptide positive vs. 9.0 (IQR 6.7 to 9.3) in pts who lost graft function ($P = 0.025$) (most recent measurement) **Health quality of life:** NA **Secondary complications of DM:** deterioration of eye disease in 4 pts, no change in peripheral neuropathy	**Procedure-related:** *Death:* 1 pt died suddenly of an accidental cause *Intra-peritoneal bleeding:* 15/65 pts (23%)((blood transfusion in 7 occasions, laparotomy in 2 pts) *PTV:* segmental branch thrombosis in 5/65 pts (8%) *Liver abnormality:* AST increased to > 2.5 times the ULN in 55% of procedures and > 5 times in 23% of procedures (usually resolved within 4 wks). Hepatic steatosis on MRI: 8/36 pts post-transplant. **Immunosuppression-related:** *Renal function (for 47 pts who completed procedure):* 5 pts progressed from micro- to microalbuminuria and 3 pts from normal progressed to microalbuminuria (17%). sCr level increased post-transplant. No significant change in CrCl, albumin excretion rate, and 24-hr protein excretion rate post-transplant *Change in IS regimen:* 10/43 pts (23%) (5 pts switched to TAC and MMF, 3 to SIR and MMF, 2 to low dose SIR, TAC, and MMF) *IS discontinuation:* not reported *Other:* mouth ulcer (89%), diarrhea (60%), acne (52%), edema (43%), ovarian cysts (very common in pre-menopausal women), pneumonia (3 pts), weight loss (common), CMV infection (2 pts had seroconversion but no overt CMV disease), cancer (1 pt had papillary carcinoma of the thyroid)

Table D.1: Summary of safety and efficacy results (continued)

Study	Patient	Intervention
Froud et al. 2005[48] University of Miami, Miami, USA Single centre	**Total No.:** 16 (2 did not complete transplantation) **Age (yr):** 40.8 ± 9.7 **Gender (M/F):** 7/9 **BMI (kg/m²):** 24.8 ± 1.7 **Duration of DM (yr):** 26.9 ± 12.4 **Hypoglycemia:** hypoglycemia unawareness in all pts **Labile diabetes:** NA **Baseline renal function:** 3 pts had nephropathy (no detail)	**Culture of islets:** 35 ± 15 (range 7.3 to 65.5) hrs **No. of infusions:** 1: 3 pts 2: 13 pts (5 pts receive supplemental transplant) 4 infusions used islets from 2 donors, 1 infusion used 3 donors. **Total IE/kg:** 13,552 ± 2,982 **Immunosuppressive regimen:** DAC, SIR, TAC Half of the pts received a single dose of infliximab **Follow-up:** up to 3 yrs
Hering et al. 2005[35] Minnesota, USA Single centre	**Total No.:** 8 pts **Age (yr):** 37 ± 3 **Gender (M/F):** 0/8 **BMI (kg/m²):** 23.0 ± 2.6 **Duration of DM (yr):** 28 ± 7 **Hypoglycemia:** 7 of 8 pts (severe) **Labile diabetes:** NA **Baseline renal function:** microalbuminuria in 4 pts	**Culture of islets:** yes **No. of infusions:** 1 infusion (using a single donor) for all pts **Total IE/kg:** 7271±1,035 **Immunosuppressive regimen:** Induction: RATG, methylpredisolone, DAC, etanercept Maintenance: SIR, MMF, or low dose TAC **Follow-up:** 1 yr

	Efficacy	Adverse events
	Insulin independence: Any time: 14/16 (88%) (1 pt with 1 infusion and 13 pts with 2 infusions) 1 yr: 11/16 pts (69%) 1.5 yrs: 6/16 pts (37%) 2 yrs: 5/16pts (31%) **Insulin requirement (U/d):** 12.6 ± 5.4 post- vs. 32.7 ± 11.2 pre-transplant (a reduction of 59 ± 18%) in 8 pts **Hypoglycemia:** no severe hypoglycemia **C-peptide secretion:** detectable in all pts while on immunosuppression **HbA1c:** returned to normal in 8 insulin independent pts over 3 yrs **Health quality of life:** NA **Secondary complications of DM:** NA	**Procedure-related:** *Death:* 0 *Intra-peritoneal bleeding:* 2/34 procedures (6%), 1 pt required blood transfusion *PVT:* 0 *Liver abnormality:* transient rise in liver transaminases followed each infusion, resolved by 2-3 wks; Fatty liver on MRI: 1/13 pts (8%) **Immunosuppression-related:** *Renal function:* sCr increased in 2 pts; 5 pts developed macroalbuminuria; all pts developed proteinuria *Change in IS regimen:* removal of TAC in 4 pts due to short-term memory loss, renal dysfunction, eczema and insomnia/depression *IS discontinuation:* 3 pts due to aspiration pneumonia, parvovirus infection, and hypereosinophilia *Other:* leucopenia/neutropenia (9 pts), new onset or exacerbation of hyperlipidemia (14/16 pts), mouth ulcer, peripheral edema and other SIR- or TAC-related side effects were common, sub-clinical CMV disease in 1 pt
	Insulin independence: Any time: 8/8 pts (100%) 1 yr: 5/8 pts (63%) **Insulin requirement:** NA **Hypoglycemia:** none in all pts over 1 yr **C-peptide secretion:** detectable in 7 of 8 pts post-transplant (time of measurement not clear) **HbA1c:** within normal range post-transplant in all pts when insulin free (time of measurement not clear) **Health quality of life:** NA **Secondary complications of DM:** NA	**Procedure-related:** *Death:* 0 *Intra-peritoneal bleeding:* 0 *PVT:* 0 *Liver abnormality:* NA **Immunosuppression-related:** *Renal function:* no clinical significant changes in CrCl or urinary albumin excretion observed *Change in IS regimen:* NA *IS discontinuation:* 0 *Other:* mouth ulcer (8 pts), lymphopenia & transient neutropenia (5 pts)

Table D.1: Summary of safety and efficacy results (continued)

Study	Patient	Intervention
Hering et al. 2004[49] Minnesota, USA Single centre	**Total No.:** 6 pts **Age (yr):** mean 33 (range 24 to 46) **Gender (M/F):** 1/5 **BMI (kg/m²):** mean 23.5 (range 22.0 to 26.7) **Duration of DM (yr):** mean 24.2 (range 13 to 35) **Hypoglycemia:** 6 pts (severe) **Labile diabetes:** NA **Baseline renal function:** microalbuminuria in 1 pt	**Culture of islets:** yes (2 days) **No. of infusions:** 1 infusion (using a single donor) for all pts **Total IE/kg:** 10,302 ± 2,594 **Immunosuppressive regimen:** Induction: hOK3γ 1 (Ala-Ala), SIR Maintenance: SIR, TAC **Follow-up:** 1 yr
Hirshberg et al. 2003[27] NIH, USA Single centre	**Total No.:** 6 pts **Age (yr):** range 39 to 63 **Gender (M/F):** 0/6 **BMI (kg/m²):** 21.7 ± 3 **Duration of DM (yr):** range 15 to 30 **Hypoglycemia:** 6 pts (severe hypoglycemia secondary to hypoglycemia unawareness) **Labile diabetes:** NA **Baseline renal function:** NA	**Culture of islets:** NA **No. of infusions:** 1: 2 pts 2: 4 pts **Total IE/kg:** NA **Immunosuppressive regimen:** DAC, SIR, TAC **Follow-up:** range 17 to 22 months

	Efficacy	Adverse events
	Insulin independence Any time: 4/6 pts (67%) 1 yr: 4/6 pts (67%) **Insulin requirement:** reduced in 2 pts (transient reduction in 1 pt) **Hypoglycemia:** none in 4 insulin independent pts **C-peptide secretion:** detectable in 4 insulin independent over 1 yr **HbA1c:** normal in 4 insulin independent pts over 1 yr **Health quality of life:** NA **Secondary complications of DM:** NA	**Procedure-related:** *Death:* 0 *Intra-peritoneal bleeding:* 0 *PVT:* 0 *Liver abnormality:* transient increase of AST in 4 pts **Immunosuppression-related:** *Renal function:* change from normoalbuminuria to macroalbuminuria in 1 pt, change from microalbuminuria to macroalbuminuria in 1 pt *Change in IS regimen:* NA *IS discontinuation:* NA *Other:* neutropenia (3 pts), generalized rash (1 pt), hOK3γ 1 (Ala-Ala) associated fever, chills and nausea, mouth ulcer, weight loss (pt number not reported)
	Insulin independence 1 yr: 3/6 pts (50%) (1 pt with 1 infusion, 2 pts with 2 infusions) **Insulin requirement:** reduced in 3 pts who were insulin dependent **Hypoglycemia:** no severe hypoglycemia in all 6 pts **C-peptide secretion:** all 6 pts demonstrated arginine stimulatable C-peptide levels for more than 1 yr post-transplant **HbA1c:** 8.2 ± 1.2 pre- vs. 6.04 ± 0.06 1 yr post-transplant (data from 6 pts) **Health quality of life:** NA **Secondary complications of DM:** NA	**Procedure-related:** *Death:* 0 *Intra-peritoneal bleeding:* 1 pt (treated in ICU) *PVT:* partial PVT in 1 pt (treated in ICU) *Liver abnormality:* NA **Immunosuppression-related:** *Renal function*: worsening in 3 pts *Change in IS regimen:* withdrawal of SIR in 1 pt due to SIR induced interstitial pneumonitis *IS discontinuation:* 2 pts (1 pt due to intolerable diarrhea, fatigue, weight loss, and deteriorating renal function, 1 pt due to loss of islet function) *Other:* mouth ulceration (6 pts), anemia (6 pts) episodic diarrhea (5 pts), leg edema (5 pts), generalized fatigue (5 pts), temporary severe neutropenia (2 pts), no CMV infection

Table D.1: Summary of safety and efficacy results (continued)

Study	Patient	Intervention
Lee et al. 2005[50] Baylor College of Medicine, Houston, USA Single centre	**Total No.:** 12 pts **Age (yr):** median 44 (range 33 to 62) **Gender (M/F):** 3/9 **BMI (kg/m²):** NA **Duration of DM (yr):** NA **Hypoglycemia:** NA **Labile diabetes:** NA **Baseline renal function:** no urinary protein present on urinalysis	**Culture of islets :** NA **No. of infusions*:** 1: 0 2: 8 pts 3: 4 pts **Total IE/kg:** NA **Immunosuppressive regimen:** DAC, SIR, TAC **Follow-up:** 1 yr for 8 pts

* Combined data from an earlier publication by Barshes et al.[68] in 2005 that reported on 11 patients.

† Data came from an earlier publication by Barshes et al. in 2005[64] that reported on 10 patients.

Higher score indicates impaired quality of life, lower score indicates no or minor impairment.

	Efficacy	Adverse events
	Insulin independence Any time: 6/12 pts (50%) **Insulin requirement:** NA **Hypoglycemia:** NA **C-peptide secretion:** increased in all pts (time for measurement not clear) **HbA1c:** median 8.7% pre- vs. 5.9% post-transplant ($P < 0.0003$) (time for measurement not clear) **Health quality of life†:** HFS Questionnaire#: total score 156 (range 49 to 170) before vs. 69 (range 0 to 170) 1 yr after first transplant ($P = 0.04$) Fatigue Questionnaire: overall, no significant change see in the total score SF-36: total score 60.8 (range 32 to 88) before vs. 77.0 (range 30 to 98) 1 yr post-transplant (nss) All component scores improved post-transplant (nss) **Secondary complications of DM:** Retinopathy: no progression when compared with pre-transplant measures in all 8 pts, improvement in 1 pt Neuropathy: improvement or stabilization of diabetic neuropathy in 50% of 8 pts	**Procedure-related*:** *Death:* 0 *Intra-peritoneal bleeding:* 0 *PVT:* 0 *Liver abnormality:* transient elevation of ALT in 11 pts **Immunosuppression-related:** *Renal function:* no urinary protein present on urinalysis *Change in IS regimen:* NA *IS discontinuation:* NA *Other:* NA

Table D.1: Summary of safety and efficacy results (continued)

Study	Patient	Intervention
Maffi et al. 2007[51] San Raffaele Scientific Institute, Milan, Italy Single centre	**Total No.:** 19 **Age (yr):** 37.2 ± 9.0 **Gender (M/F):** 10/9 **BMI (kg/m²):** NA **Duration of DM (yr):** 23.3 ± 9.0 (range 11 to 37) **Hypoglycemia:** decrease hypoglycemia awareness in all pts **Labile diabetes:** NA **Baseline renal function: nephropathy:** 2 pts (1 pt had macroproteinuria, the other had elevated sCr)	**Culture of islets:** yes **No. of infusions:** 1: 2 pts 2: 11 pts 3: 6 pts **Total IE/kg:** 11,477 ± 3,970 **Immunosuppressive regimen:** DAC, SIR, TAC, MMF **Follow-up:** 1 yr: 17 pts 2 yrs: 8 pts

* Data from an earlier publication by Venturini et al. in 2006[66] that reported on 10 patients

† Data from an earlier publication by Bertuzzi et al. in 2004[69] that reported on 14 patients

	Efficacy	Adverse events
	Insulin independence: 1 yr: 8/19 pts (42%) (interpreted from Figure 1) **Insulin requirement:** NA **Hypoglycemia:** no severe hypoglycemia post-transplant even with insulin therapy **C-peptide secretion (nmol/l):** fasting C-peptide Pre-transplant: 0.01 ± 0.01 1 yr post-transplant: 0.46 ± 0.07 ($P < 0.001$ vs. pre-transplant) 2 yrs post-transplant: 0.50 ± 0.03 ($P < 0.001$ vs. pre-transplant) **HbA1c (%):** Pre-transplant: 8.6 ± 0.03 1 yr post-transplant: 6.8 ± 0.2 ($P < 0.001$ vs. pre-transplant) (based on 17 pts) 2 yrs post-transplant: 6.4 ± 0.2 ($P < 0.02$ vs. pre-transplant) (based on 8 pts) **Health quality of life:** NA **Secondary complications of DM*:** Retinopathy: increased blood flow velocities of central retina artery and central retina vein at 1-yr follow-up (ss)	**Procedure-related†:** *Death:* NA *Intra-peritoneal bleeding:* 3 pts *PVT:* small portal branch in 1 pt *Liver abnormality:* AST & ALT increased in 10/14 pts (71%); higher elevation after the 1st transplant, compared with the 2nd and 3rd transplants; returned to normal within 2 months after transplant **Immunosuppression-related:** *Renal function:* sCr increased in 2 pts and progressed to ESRD despite withdrawal of immunosuppressive drugs; CrCl remained within normal range for pts with normal baseline CrCl, decreased in 2 pts with decreased baseline values. 24-hr UPE worsened (> 300mg/24 hrs) in 4 pts *Change in IS regimen:* 6 pts changed from SIR to MMF because of mouth ulcer, joint pain, or edema; 1 pt changed from TAC to cyclosporine because of tremor. *IS discontinuation:* 4 pts (2 pts due to deterioration of renal function, 1 pt due to intolerance to immunosuppression, 1 pt due to graft failure) *Other:* NA

Table D.1: Summary of safety and efficacy results (continued)

Study	Patient†	Intervention
Keymeulen et al. 2006[52] Brussels, Belgium (Data collected from two hospitals)*	**Total No.:** 24 pts **Age (yr):** median 43 (IQR 34 to 39) **Gender (M/F):** 13/9 **BMI (kg/m²):** median 24 (IQR 22 to 26) **Duration of DM (yr):** median 24 (IQR 18 to 33) **Hypoglycemia:** not clear **Labile diabetes:** not clear **Baseline renal function:** microalbuminuria in 7 pts, macroalbuminuria in 1 pt	**Culture of islets:** yes **No. of infusions:** 1: 9 pts 2: 13 pts **Total IE/kg:** NA **Immunosuppressive regimen:** ATG, MMF, TAC **Follow-up:** 1 yr
Badet et al. 2007[53] Swiss-French GRAGIL group Multicentre	**Total No.:** 10 pts **Age (yr):** 50 ± 3 **Gender (M/F):** 6/4 **BMI (kg/m²):** 22.1 ± 0.8 **Duration of DM (yr):** 29 ± 4 **Hypoglycemia:** frequent hypoglycemia episodes in all 10 pts **Labile diabetes:** NA **Baseline renal function:** NA	**Culture of islets:** yes **No. of infusions:** 1: 2 pts 2: 8 pts **Total IE/kg:** 11,089 ± 505 (1 pt was excluded from the calculation) **Immunosuppressive regimen:** DAC, SIR, TAC **Follow-up:** median 24 (range 12 to 36, IQR 13 to 30) months

* Dr. Pipeleers, personal communication, May 2008

† 24 patients received ITA and were included in the safety analysis; Patient characteristics were based on data from 22 patients who were included in 1-yr metabolic analysis.

Continuous variables are expressed as mean ± SE unless otherwise indicated.

	Efficacy	Adverse events
	Insulin independence: 1 yr: 10/24 pts (42%) **Insulin requirement:** significantly lower at 1 yr in 8 insulin dependent pts ($p < 0.01$) **Hypoglycemia:** no severe hypoglycaemia episodes in 18 pts with C-peptide ≥ 0.5ng/ml **C-peptide secretion:** ≥ 0.5ng/ml in 18 pts at 1 yr **HbA1c (%):** lower than 6% in 10 insulin independent pts at 1 yr ($P < 0.01$) **Health quality of life:** NA **Secondary complications of DM:** NA	**Procedure-related:** *Death:* 0 *Intra-peritoneal bleeding:* 0 *PVT:* 0 *Liver abnormality:* ALT increased in 8/24 pts (33%) **Immunosuppression-related:** *Renal function:* CrCl 16% lower over 1 yr post-transplant; none presented sCr > 2 mg/dl; Albuminuria decreased in 8/8 pts with pre-transplant micro- or macroalbuminuria. *IS change:* NA *IS discontinuation:* 1 pt due to MMF-caused gastrointestinal symptoms *Other:* fever (8 pts), pyrosis (heartburn) (9 pts), cerebellar ataxia (1 pt), CMV hepatitis (1 pt), leucopenia (17 pts at 3 months and 6 pts at 1 yr), weight loss (22 pts)
	Insulin independence: One month: 8/10 pts (80%) 6 months: 6/10 pts (60%) 1 yr: 3/10 pts (30%) **Insulin requirement (U/day):** 30.5 ± 2.8 pre-transplant vs. 7.8 ± 3.3 1 yr post-transplant ($P < 0.001$) **Hypoglycemia:** number of episodes/month: 18 ± 4 pre-transplant, 2 (in 1 pt) at 6 months, 4 (1 pt) and 20 (1 pt) at 1 yr **C-peptide secretion (ng/ml):** basal 1.19 ± 0.22 at 1 yr ($P < 0.001$ vs. pre-transplantation), > 0.3 in all pts, > 0.5 in 8/10 pts **HbA1c (%):** 8.58 ± 0.47 pre- vs. 6.65 ± 0.17 1 yr post-transplant ($P < 0.002$); improved in all pts; ≤ 6.2 in 3 insulin independent pts at 1 yr **Health-related quality of life:** NA **Secondary complications of DM:** NA	**Procedure-related:** *Death:* 0 *Intra-peritoneal bleeding:* 1 pt (10%) *PVT:* segmental branch1 in 1 pt (10%) *Liver abnormality:* liver transaminases increased in 1 pt (10%) and returned to normal within 1 month. **Immunosuppression-related:** *Renal function:* NA *Change in IS regimen:* TAC to MMF because of acute optic neuropathy (1 pt) *IS discontinuation:* 0 *Other:* NA

Table D.1: Summary of safety and efficacy results (continued)

Study	Patient	Intervention
O'Connell et al. 2006[54] University of Sydney at Westmead Hospital, Westmead, Australia Single centre	**Total No.:** 6 pts **Age (yr):** mean 42 (range 33 to 50) **Gender (M/F):** NA **BMI (kg/m²):** NA **Duration of DM (yr):** mean 23.8 (range 8 to 37) **Hypoglycemia:** 6 pts (severe hypoglycemia unawareness) **Labile diabetes:** NA **Baseline renal function:** 2 pts had microalbuminuria	**Culture of islets:** NA **No. of infusions:** 1: 1 pt 2: 5 pts **Total IE/kg:** mean 17,958 (range 6,995 to 26,480) **Immunosuppressive regimen:** DAC, SIR, TAC **Follow-up:** median 18 (range 3 to 31) months

	Efficacy	Adverse events
	Insulin independence: Any time: 3/6 pts (50%) 1 yr: 2/6 pts (33%) 2 yrs: 2 pts (33%) (back to insulin therapy after 2 yrs) **Insulin requirement:** reduced in 5 pts after the 1st infusion **Hypoglycemia:** mild episodes in 3 pts; severe hypoglycemia episodes in 1 pt after discontinuation of immunosuppressive treatment after graft loss and in 1 pt who never achieved any graft function **C-peptide secretion (nmol/L):** detectable in 5 pts (≥ 0.3) **HbA1c (%):** reduced in all pts, mean 8.4 (range 7.8 to 9.7) pre- vs. mean 7.2 (range 5.5 to 9.2) 1 yr post-transplant (< 6.0 in only 1 pt) **Health quality of life:** 3 of 4 pts who were not working pre-transplant returned to work post-transplant. **Secondary complications of DM:** NA	**Procedure-related** *Death:* 0 *Intra-peritoneal bleeding:* 1 pt (requiring blood transfusion and laparotomy) *PVT:* partial in 1 pt, complete in 1 pt (withdrawn from the study) *Liver abnormality:* mild rise (< 2-fold increase) in ALT in all pts (100%); hepatic steatosis on ultrasound in 2/6 pts (33%) **Immunosuppression related** *Renal function:* GFR significantly decreased in 1 pt at 18 months (from 143 to 63 ml/min/1.73 m^2), which required cessation of TAC and substitution with MMF *Change in IS regimen:* TAC was switched to MMF in 1 pt due to decrease in renal function *IS discontinuation:* 1 pt due to intolerance of immunosuppression-related nausea and mouth ulcer *Other:* mouth ulcer, raised cholesterol level, ankle swelling (pt number not reported), skin squamous cell carcinoma 3 months post transplant in 1 pt (could have been present before the immunosuppressive treatment), presumed recurrence of tuberculosis in 1 pt.

Table D.2: Summary of case series on safety only

Study	Patient
O'Connell et al. 2006[54] University of Sydney at Westmead Hospital, Westmead, Australia Single centre	**Total number:** 67 **Age (yr):** 43.3 ± 9.9 **Gender (M/F):** 28/39
Markmann et al. 2003[59] University of Pennsylvania Health system, Philadelphia	**Total No.:** 4 **Age (yr):** NA **Gender (M/F):** NA
Molinari et al. 2005[60] University of Alberta Edmonton	**Total No.:** 2 **Age (yr):** 40, 49 **Gender (M/F):** 0/2
Senior et al. 2007[61] University of Alberta, Edmonton	**Total No.:** 41 **Age (yr):** 43 ± 9.8 (range 24 to 64) **Gender (M/F):** 20/21
Andres et al. 2005[55] Geneva University Hospital, Geneva	**Total No.:** 5 **Age (yr):** mean 42.8 (range 28 to 58) **Gender (M/F):** 4/1
Cure et al. 2004[62] University of Miami School of Medicine, Miami	**Total No.:** 13 **Age (yr):** mean 41 (range 24 to 55) **Gender (M/F):** 0/13
Yakubovich et al. 2007[63] University of British Columbia, Vancouver	**Total No.:** 23 **Age (yr):** NA **Gender (M/F):** NA

	Safety
	Procedure-related *Death:* 0 *Bleeding:* 18 events (13.6% of 132 procedures) occurred in 17 pts (25.4%). 3 pts required surgical treatment *PVT:* 5 events (3.8% of 132 procedures)
	Liver abnormality Hepatic steatosis on MRI: 2 pts
	Immunosuppression-related Small bowel ulceration following SIR therapy in 2 pts, complete resolution after withdrawal of SIR
	Immunosuppression-related Renal function *Decline in eGFR:* At 1 yr: 47% (17/36) At 2 yrs: 64% (16/25) At 3 yrs: 92% (11/12) At 4 yrs: 80% (4/5) Compared with pre-transplant, mean eGFR was unchanged at 1 yr, significantly lower at 2 yrs and 3 yrs, but not statistically different from baseline at 4 yr follow-up *Changes in albuminuria status:* Microalbuminuria: 9 pts (22%) post- vs. 4 pts (10%) pre-transplant ($P<0.001$) Macroalbuminuria: 6 pts (15%) post- vs. 3 pts (7%) pre-transplant ($P<0.001$)
	Immunosuppression-related Renal function *CrCl:* decrease in 2 pts *Albuminuria:* increased in 2 pts
	Immunosuppression-related Change in female reproductive system *Menstrual cycle pattern change:* 6 pts changed from regular to irregular *Ovarian cysts:* 8 (61.5%) pts
	Immunosuppression-related CMV infection: 3 pts developed CMV antigenemia following islet transplant despite receiving prophylaxis treatment.

Table D.3: Comparison of islet transplantation with intensive insulin treatment

Study	Patient	Intervention
Fung et al. 2007[57] University of British Columbia, Vancouver Prospective, cross over design **Objective:** to compare intensive medical therapy with islet transplantation on the progression of nephropathy	**Total No.:** 21 in ITA vs. 44 in medical group **Age (yr):** 46.3 ± 9.5 in ITA vs. 46.5 ± 8.5 in medical group **Gender (M/F):** 10/11 in ITA vs. 21/23 in medical group **BMI (kg/m²):** 24.9 ± 2.0 in ITA vs. 25.8 ± 3.5 in medical group **Duration of DM (yr):** 33.5 ± 8.7 in ITA vs. 30.2 ± 9.2 in medical group **Hypoglycemia:** only 1 pt in ITA group **GFR (ml/min/1.73m²):** 108 ± 22 in ITA vs. 116 ± 31 in medical group **ACR (mg/mmol):** median: 2.6 (IQR 1.5 to 5.6) in ITA vs. 8.3 (3.1 to 25.4) in medical group (nss) **Overt proteinuria:** 6 pts in ITA vs. 6 pts in medical group	**Procedure:** ITA *No. of infusions:* total 50 (1 to 3 infusions/patient) *Total IE/kg:* 13,754 ± 2987 *Immunosuppressive regimen:* initially maintenance with TAC and SIR, then changed to TAC and MMF **Comparator:** intensive medical therapy including glucose management (insulin), angiotensin blockade, and control of lipids and blood pressure **Follow-up (median):** 29 months (range 13 to 45) in ITA group vs. 29.5 months (range 13 to 56) in medical group

Table D.4: Comparison of islet transplantation with whole organ pancreas transplantation

Study	Patient	Intervention
Frank et al. 2004[23] Retrospective analysis University of Pennsylvania **Objective:** to compare the efficacy, risks, and costs of pancreas transplantation with the costs of islet transplantation in the treatment of patients with type 1 diabetes mellitus	**Total No.:** 43 Islet transplantation 13 (ITA: 9 pts, IAK: 4 pts) WOP: 30 (SPK: 25 pts, PAK: 5 pts) **Age (yr):** mean 42 in ITA vs. 40 in WOP (nss) **Gender (% female):** 44% in ITA vs. 33% in WOP (nss) **BMI (kg/m²):** 24.2 in ITA vs. 23.7 in WOP (nss) **Duration of DM (yr):** 28 in ITA vs. 27 in WOP (nss) **History of dialysis:** 0 in ITA vs. 73% in WOP (P ≤ 0.01) **Labile diabetes:** highly liable diabetes in all ITA recipients **Hypoglycemia:** Recurrent episodes of severe hypoglycemic unawareness in all ITA recipients	**Procedure:** ITA *No. of infusions:* NA *Total IE/kg:* NA *Immunosuppressive regimen:* Edmonton protocol: induction with Zenapax, maintenance with TAC and SIR **Comparator:** WOP *Immunosuppressive regimen:* induction with thymoglobulin and maintenance with tacrolimus, mycophenolate, and steroids **Donor:** older and heavier for ITA than for WOP **Follow-up:** Median 421 days for WOP vs. 522 days for islet transplantation (nss) (range not reported)

*Efficacy data for ITA were not reported separately.

†Based on 11 pts; 2 pts who never achieved insulin independence and 1 pt with functioning graft who were withdrawn from the study were excluded from this analysis.

§ Based on 26 pts; 4 pts with graft loss caused by technical problems or death were excluded from this analysis.

	Efficacy
	Insulin independence: Any time: 17 pts (4 to 45 months) in ITA group, not applicable for medical group **Hypoglycemia:** NA **Level of C-peptide (ng/ml):** NA **HbA1c levels (%):** median 6.6 in ITA vs. 7.3 in medical control (P < 001) **Health quality of life:** NA **Secondary complications of DM:** *Change in GFR (ml/min/month/1.73m2):* -0.31 ± 1.18 (95% CI: -0.61 to -0.01) in ITA vs. -0.35 ± 0.89 (95% CI: -0.57 to -0.13) in medical group (nss) *Estimated GFR:* no difference between ITA and medical group *ACR (median):* 1.8 (IQR: 1 to 4) in ITA vs. 1.6 (IQR: 0 to 4.9) in medical group (nss) *Proteinuria:* ITA: of 6 pts with pre-transplant overt proteinuria, 1 pt regressed to microalbuminuria, 3 pts had persistent microalbuminuria, and 2 pts had normal ACR; 1 pt from microalbuminuria to overt proteinuria. Medical: 1 pt from microalbuminuria to overt proteinuria; of 6 pts with overt proteinuria, 2 pts remained unchanged, 3 pts regressed to microalbuminuria, 1 pt reverted to normal.

	Efficacy*	Adverse events
	Insulin independence: 1 yr: 56% in islet transplantation† 2 yrs: 100% in WOP§ 5 yrs: NA 5/12 islet transplantation pts remained normoglycemic and completely insulin independent from 3 months to 2.5 yrs post-transplantation; 25 of 30 WOP recipients continued to function normally. **Insulin requirement:** reduced post-transplant **C-peptide secretion (ng/ml):** 1.7 in islet transplantation vs. 3.9 in WOP (P < 0.001) during the first 600 days post-transplant **HbA1c (%):** 6.3% in islet transplantation vs. 5.0% in WOP (P ≤ 0.001) during the 1st yr **Hypoglycemia:** none of pts with graft function had hypoglycaemic episode **Health quality of life:** NA **Secondary complications of DM:** NA	**Procedure-related:** *Death:* 0 in ITA vs. 1 in WOP (unknown cause) *Pts requiring post-transplant surgery:* 0 in ITA vs. 7 (23%) in WOP (nss) *Intra-peritoneal bleeding:* 0 in ITA vs. 13 pts (43%) in WOP (P ≤ 0.025) (requiring blood transfusion) *PVT:* NA *Liver abnormality:* hepatic steatosis on imaging in 3 pts in ITA (not available for WOP) **Immunosuppression-related:** *Renal function:* most ITA recipients demonstrated a mild decline in their renal function. *IS discontinuation:* 2 ITA recipients (1 pt due to traumatic foot injury and poor healing after surgery, 1 pt due to severe painful mouth ulcer) *Change in IS regimen:* NA *Other:* mouth ulceration: 9 pts in ITA vs. 0 in WOP (P < 0.001) CMV infection: 0 in ITA vs. 3 pts (10%) in WOP (nss)

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The purpose of this report is to update an earlier HTA report published in 2003. This report examines the newly published clinical research evidence on the safety and efficacy/effectiveness of islet transplantation in type 1 diabetic patients who have severe hypoglycemia episodes or hyperglycemia unawareness but are without kidney failure. The main clinical efficacy/effectiveness outcomes, insulin independence and/or decrease in hypoglycemia events as a result of the Edmonton protocol, are considered over at least a one-year term or longer.

IHE
INSTITUTE OF
HEALTH ECONOMICS
ALBERTA CANADA

Institute of Health Economics
1200 - 10405 Jasper Avenue
Edmonton AB Canada T5J 3N4

Tel. 780.448.4881 Fax. 780.448.0018
info@ihe.ca

www.ihe.ca

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