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World J Gastroenterol 2007 December 21; 13(47): 6347-6355
World Journal of Gastroenterology ISSN 1007-9327

TOPIC HIGHLIGHT

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Transplantation for the treatment of type 1 diabetes

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Received: June 15, 2007 Revised: August 8, 2007

Abstract

Transplantation of pancreatic tissue, as either the intact whole pancreas or isolated pancreatic islets has become a clinical option to be considered in the treatment of patients with type 1 insulin-dependant diabetes mellitus. A successful whole pancreas or islet transplant offers the advantages of attaining normal or near normal blood glucose control and normal hemoglobin A1c levels without the risks of severe hypoglycemia associate with intensive insulin therapy. Both forms of transplants are also effective at eliminating the occurrence of significant hypoglycemic events (even with only partial islet function evident). Whereas whole pancreas transplantation has also been shown to be very effective at maintaining a euglycemic state over a sustained period of time, thus providing an opportunity for a recipient to benefit from improvement of their blood glucose control, it is associated with a significant risk of surgical and post-operative complications. Islet transplantation is attractive as a less invasive alternative to whole pancreas transplant and offers the future promise of immunosuppression-free transplantation through pre-transplant culture. Islet transplantation however, may not always achieve the sustained level of tight glucose control necessary for reducing the risk of secondary diabetic complications and exposes the patient to the adverse effects of immunosuppression. Although recent advances have led to an increased rate of obtaining insulin-independence following islet transplantation, further developments are needed to improve the long-term viability and function of the graft to maintain improved glucose control over time.

Key words: Type 1 diabetes; Insulin-dependant diabetes mellitus; Pancreas transplantation; Pancreatic islet transplantation; Immunosuppression; Glucose control

Meloche RM. Transplantation for the treatment of type 1 diabetes. *World J Gastroenterol* 2007; 13(47): 6347-6355

http://www.wjgnet.com/1007-9327/13/6347.asp

TRANSPLANTATION FOR THE TREATMENT OF TYPE 1 DIABETES

It has been clearly shown that patients with type 1 insulin-dependent diabetes mellitus (IDDM) benefit from improved blood glucose control. In 1993, the Diabetes Control and Complications Trial Research Group reported that patients with IDDM treated with intensive insulin therapy showed a reduced risk of developing retinopathy, albuminuria or microalbuminuria and clinical neuropathy when compared to patients who received conventional insulin therapy[1]. In this trial the intensive therapy group was shown to have achieved sustained lowered blood glucose concentrations over time as reflected by significantly lower glycosylated hemoglobin values compared to those of the conventional insulin therapy group. Although the intensive therapy group benefited from reduced long-term complications, the risk of severe hypoglycemia associated with tight glycemic control was three times greater than in the conventional therapy group.

Transplantation of pancreatic tissue, as either the intact whole pancreas or isolated pancreatic islets has become a clinical option to be considered in the treatment of patients with IDDM. Successful pancreatic transplantation offers the advantages of attaining normal or near normal blood glucose control without the risks of severe hypoglycemia associated with intensive insulin therapy. Pancreatic transplantation however, may not always achieve the sustained level of tight glucose control necessary for reducing the risk of secondary diabetic complications and exposes the patient to peri-operative or procedural risks, the adverse effects of immunosuppression and the risk of an eventual significant loss of graft function necessitating a return to exogenous insulin.

When either transplantation of a whole pancreas or pancreatic islets is being offered for the treatment of IDDM, the goals of the program should include: (1) A transplant procedure, which can be performed with overall low morbidity and mortality and subject the recipient to a minimal degree of side effects and complications of the post-procedural care; (2) Elimination of the need for insulin administration and close blood glucose monitoring; (3) Eliminate the occurrence of significant hypoglycemic events; (4) Creation of a euglycemic state, with preprandial and postprandial blood glucose concentrations and

hemoglobin A1c levels comparable to those in the non-diabetic population; (5) Achieving sustained effect of the transplant as to maintain normal glucose homeostasis over time.

WHOLE PANCREAS TRANSPLANTATION

Whole pancreas transplantation, first performed in 1966 in combination with a kidney in IDDM patients suffering from end-stage renal failure, demonstrated that a euglycemic state could be obtained without the need for exogenous insulin[2]. The early procedures however, were complicated by a high morbidity rate; early graft failure and poor patient survival and few transplants were performed[3]. Improvements in transplant techniques, immunosuppression therapies and post-transplant monitoring of graft function and rejection has resulted in a dramatic improvement in patient morbidity and graft survival. With the improved outcomes and demonstrated efficaciousness in controlling the diabetic glycemic state, whole pancreas transplantation is now recognized by the American Diabetes Association as an acceptable therapeutic alternative to continued insulin therapy in diabetic patients with imminent or established end-stage renal disease who had or plan to have a kidney transplant[4].

Pancreas transplantation may be considered as a group of three separate, clinical entities: simultaneous pancreas and kidney transplant (SPK), pancreas after kidney transplant (PAK) and pancreas transplant alone (PTA). Each form of transplant is characterized by its own indications, risks and outcomes.

Simultaneous pancreas kidney transplantation

Diabetes is a major cause of renal disease and is associated with approximately 40% of new cases of end-stage renal failure (ESRF) in the US, who will subsequently require renal dialysis or kidney transplantation[5]. When an IDDM patient develops ESRF and requires a kidney transplant; consideration is now commonly given to whether the patient would also benefit from receiving a pancreas transplant. SPK transplantation is the most common form of pancreas transplantation performed accounting for 60% of the total number of pancreas transplants performed each year in the US (approximately 900/year)[6-8]. The annual number of SPK transplants has remained stable over the last 10 years, however this may reflect the increasing interest in the option of PAK transplantation (living donor kidney transplantation) by the patient in ESRF with IDDM.

When SPK transplantation is performed, the patient undergoes only one operation and following the surgery may be managed on the same (or very similar) immunosuppressive drugs they would have received for a renal transplant alone. The combined procedure offers excellent patient and pancreatic graft survival, producing a sustained euglycemic state off of exogenous insulin or oral hyperglycemic agents[7,9]. The renal transplant provides an effective method of surveillance of both grafts for acute rejection (creatinine clearance, biopsy) and may in part explain the improved one-year and long-term pancreatic graft survival rates when compared to a pancreas transplant without a donor-matched kidney transplant. There also has been no evidence that the pancreas transplant may have a deleterious effect on the simultaneously transplanted kidney.

Pancreas after kidney transplantation

As the number of patients with ESRF increased in the past decade, the demand for renal transplantation outpaced the supply of cadaveric kidneys available. By 2000, the number of living donor kidney transplants performed in the US exceeded the number of cadaveric donor transplants. Whereas SPK transplantation is usually restricted to the use of cadaveric kidneys only, PAK transplantation offers the option of using a living donor kidney, and in doing so both expands the number of kidneys available for transplant and allows the diabetic patient the opportunity to benefit from early living donor kidney transplant (better long term outcome, avoidance of dialysis). With improved surgical technique, better immunosuppressive drugs and rejection monitoring, outcomes for solitary pancreas transplants have improved such that PAK transplantation is now routinely considered[6,7]. The kidney transplant recipient is required to demonstrate stable renal function and minimal post procedure complications to be acceptable for subsequent pancreas transplantation. The PAK transplant option does require the patient to undergo two major operations, however the post transplant immunosuppression and care are similar to kidney transplant alone.

Pancreas transplantation alone

PTA is offered in some transplant centers to IDDM patients who have difficult to manage diabetes and suffer from severe hypoglycemic episodes (often with hypoglycemic unawareness) with little or no evidence of renal disease. As with PAK transplantation, improvements in PTA graft survival has significantly improved in recent years, although the question of whether or not the procedure may have an adverse long term affect on the recipients renal function (calcineurin antagonist based immunosuppression) has not been resolved. The normalizing of blood glucose levels with the pancreas transplant may offer this patient group the possibility of long-term improvement in renal function. The American Diabetes Association's 2006 Position Statement on pancreas and islet transplantation recommends "In the absence of indications for kidney transplantation, pancreas-alone transplantation should only be considered a therapy in patients who exhibit these three criteria: (1) a history of frequent, acute and severe metabolic complications (hypoglycemia, marked hyperglycemia, ketoacidosis) requiring medical attention; (2) clinical and emotional problems with exogenous insulin therapy that are so severe as to be incapacitating; and (3) consistent failure of insulin-based management to prevent acute complications"[4]. Since 2001, PTA has accounted for approximately 12% of pancreas transplants performed annually in the US[6].

WHOLE PANCREAS TRANSPLANTATION SURGERY

Bladder verses enteric pancreatic drainage

In the early development of pancreas transplantation, the surgical procedure involved drainage of the exocrine pancreas secretions in to the bladder. This was best accomplished by transplanting (in continuity) a short segment of donor duodenum with the pancreas, which provides a conduit from the pancreas to the bladder through which the secretions could be drained. Use of the duodenum-to-bladder drainage reduced the rate of transplant exocrine secretion leaks and allowed monitoring for evidence of early graft rejection by the frequent measurement of amylase activity in the urine. Direct biopsy of the transplanted pancreas and duodenum by cystoscopic technique could also be performed[3]. However, the loss of bicarbonate-rich pancreatic secretions into the bladder is associated with a number of problems. Patients who have undergone bladder drainage of their pancreas transplant require daily oral bicarbonate and fluid replacement to offset the severe metabolic acidosis and at times significant fluid loss associated with the procedure. Other problems associated with bladder drainage include: reflux graft pancreatitis (bladder dysfunction associated with diabetic neurogenic bladder); cystitis; urethritis and stricture formation; recurrent bladder infections. For some patients (approximately 15% at three years from the time of transplantation) the complications were severe enough that surgical reversal of the bladder drained pancreas transplant, with re-direction of the secretions into the small bowel was necessary[3,9].

In the late nineties transplant centers began to perform primary enteric drainage of pancreatic secretions in order to avoid the complications of bladder drainage. Improvements in immunosuppression had led to a reduced number of episodes of acute graft rejection and increasing experience with direct percutaneous needle biopsy reduced the need for urinary amylase monitoring. Enteric drainage of pancreatic secretions prevented the obligatory loss of sodium bicarbonate and fluid and the subsequent hypovolemia, metabolic acidosis and the other complications associated with bladder drainage. Initially the procedure often involved anastomosis of the transplant duodenal segment to a Roux-en-Y limb of the recipient's mid-small bowel to reduce the likelihood of an anastomotic leak, however the surgery is now routinely performed directly to the small bowel. Enteric drainage of the pancreatic transplant secretions is now the more commonly performed procedure, used in 81% of SPK, 67% of PAK and 56% of PTA transplants performed in the US during 2000-2004 (when a SPK was performed, the donor-matched kidney may be followed for evidence of acute graft rejection which may be a better early marker than urinary amylase output)[6-10].

Systemic verses portal venous drainage

Vascular drainage of the pancreas transplant may be performed either into the systemic venous system (most commonly used is the external iliac vein) or into the portal venous system (using a vein of the small bowel mesentery). With systemic venous drainage the insulin secreted by the pancreas transplant avoids early hepatic extraction and results in an elevation of both basal and stimulated serum insulin concentrations. Portal venous drainage directs the insulin released by the pancreas transplant initially to the liver in a fashion similar to the release of insulin in a non-diabetic person. Although it is felt to be "more physiological", portal venous drainage of the pancreas transplant has not been shown to offer any advantage over systemic venous drainage in maintaining normal glucose homeostasis or lipid metabolism. It has been suggested that direct presentation of the pancreas transplant alloantigen to the liver may provide an immunologic benefit. However, registry data has not found evidence for improved graft survival when portal venous drainage has been performed. Systemic venous drainage remains the more commonly performed procedure, used in 77% of SPK, 73% of PAK and 56% of PTA transplants performed in the US during 2000-2004[6-9].

Surgical complications

The complexity of the whole pancreas transplant procedure, along with the likelihood of pre-existing disease secondary to their IDDM, exposes the recipient to a variety of significant operative and post-operative risks. The extent of the post-operative problems likely limited the widespread acceptance of pancreas transplantation in the early era of its development. Serious surgical complications following the procedure include: thrombosis of graft vessels, intra-abdominal hemorrhage, anastomotic leak (enteric or bladder), graft pancreatitis, pancreatic fistula formation and intra-abdominal sepsis, all of which may require re-laparotomy and the possibility of graft loss. In recent years, with improvements in donor and recipient selection criteria, surgical technique, immunosuppression protocols (reduced incidence of early, acute rejection) and prophylaxis regimes (anti-viral, anti-bacterial and antithrombosis), there has been a significant decrease in the overall incidence of serious complications and the rate of re-laparotomy[11,12].

Immunosuppression

Since 2000, in the US the most common primary protocol for maintenance immunosuppression for whole pancreas transplantation is Tacrolimus and Mycophenolate Mofetil (MMF), although other agents such as Cyclosporine, Sirolimus and Azathioprin in varying combinations are also being used in a small number of centers[7,8]. In addition, the majority of transplant centers continue to use corticosteroids, although there is an movement towards "steroid-free" immunosuppression protocols in an attempt to reduce their adverse effects (glucose control, dyslipidemia, bone loss) in the diabetic patient transplant population. The initial success with pancreatic islet transplantation in 2000 was obtained using an immunosuppression protocol of Sirolimus and Tacrolimus in combination and avoiding steroid entirely[13]. Sirolimus has proven to be difficult to use in some patients (mouth ulcers, hyperlipidemia)[14] and recent studies

have demonstrated poorer graft survival and inferior renal function when Sirolimus is used as a primary agent in combination with Tacrolimus when compared with the use of Tacrolimus and MMF in kidney and heart transplantation[15-17]. Induction immunosuppression is routinely used in whole pancreas transplantation, with > 75% of recipients receiving either: (1) a T-cell depleting polyclonal antibody (Thymoglobulin, ATGAM) or monoclonal antibody (OKT3, Campath), (2) a non-depleting monoclonal anti-CD25 antibody (Zenapax, Simulect), or (3) both[7,8].

Long-term use of immunosuppression is associated with a number of significant side effects and complications. The side effects most commonly seen with standard maintenance immunosuppression include: nephrotoxicity, hypertension, hyperlipidemia, microvascular disease, glucose intolerance, gastrointestinal problems, weight gain, skin changes/alopecia/hirsutism[18]. Immunosuppression-relate complications include: infections (viral, bacterial, fungal, parasitic) and malignancy (skin, lymphoproliferative, genitourinary). The risk of infection depends upon the degree of immune compromise created by the immunosuppressive regiment and the exposure to possible pathogens, either through re-activation of pre-existing infection (e.g., viral, tuberculosis) or introduction by the transplant process (e.g., surgical technique, transfer from donor)[19]. The risk of skin cancer for a patient on immunosuppression following renal transplantation is cumulative, ranging from 10% to 40% at 10 and 20 years respectively (ratio of squamous cell to basal cell carcinoma 2:1)[20]. The overall prevalence of post-transplant lymphoproliferative disease and leukemia varies from 1% to 2%[21].

OUTCOMES OF WHOLE PANCREAS TRANSPLANTATION

Patient and graft survival

Whole pancreas transplantation has proven to be a safe procedure with a 1 year and 3 year patient survival rates for all forms of pancreas transplant (SPK, PAK, PTA) in the US since 1998 at about 95% and 89% respectively (unadjusted patient survival rates, 2005 OPTN/SRTR Annual Report)[6] (Table 1). Transplantation of a pancreas simultaneously with a kidney may also increase long-term IDDM patient survival compared to kidney transplantation alone. Whereas the mortality risk is increased over the first 18 months for the SPK recipient (associated with an increased rate of complications such as infection when compared to kidney transplant alone), when the pancreas continues to function post transplant, recipient survival is superior to SPK recipients who have had their pancreas graft fail or diabetic patients who received only a cadaveric kidney transplant[22,23].

One and 3 year graft survival rates for SPK transplant in the US since 1998 for kidney are ⩾ 91% and ⩾ 83% and pancreas are ⩾ 82% and ⩾ 75% respectively. Pancreas graft survival rates for PAK and PTA over a similar period were slightly less that for SPK: for 1 year 72% to 81% and 74% to 83% respectively, and at 3 years 63% to 71% and 60% to 69% respectively (unadjusted graft survival rates, 2005 OPTN/SRTR Annual Report). Although the incidence of acute kidney graft rejection has been shown to be greater following SPK than for kidney transplant alone (15% *versus* 9%), patients following SPK transplantation as a group general demonstrate better kidney graft function. This advantage of SPK on renal function disappears however when the analyses are adjusted for donor and recipient variables[9].

Table 1 Unadjusted patient and graft survival following SPK, PAK or PTA by year of transplant at 1 and 3 years

			Year of transplant					
		Survival (%)	1998	1999	2000	2001	2002	2003
SPK	Patient	One year	93.9	94.8	95.1	94.1	94.8	95.5
		Three years	89.6	90.6	90.2	89.6	+	+
PAK	Patient	One year	94.5	94.4	96.0	95.2	95.7	95.5
		Three years	90.8	88.1	91.2	89.1	+	+
PTA	Patient	One year	96.8	97.3	99.1	97.5	97.6	94.5
		Three years	90.5	90.9	95.5	90.8	+	+
SPK	Pancreas	One year	82.7	83.1	84.0	85.0	85.4	85.8
		Three years	75.8	76.0	77.0	78.9	+	+
	Kidney	One year	91.2	91.5	92.5	91.5	91.2	91.7
		Three years	83.9	83.0	83.5	83.7	+	+
PAK	Pancreas	One year	72.0	80.3	74.0	81.8	77.3	77.9
		Three years	63.4	66.8	62.3	71.5	+	+
PTA	Pancreas	One year	79.2	83.3	75.3	78.3	79.3	74.4
		Three years	60.3	69.3	60.5	64.4	+	+

Source: 2005 OPTN/SRTR annual report.

CONSEQUENCES OF WHOLE PANCREAS TRANSPLANTATION

Blood glucose control

Successful whole pancreas transplantation produces a normoglycemic state in the majority of recipients, usually within minutes of completion of the procedure without the need for exogenous insulin. Transient hypoglycemia may occur over the first 24 h requiring I.V. glucose support. Patients demonstrate normal fasting and post-prandial blood glucose concentrations and a lowering of hemoglobin A1c to normal levels. Where systemic venous drainage of the pancreas has been performed, fasting and meal-stimulated insulin concentrations are elevate, the likely result of the elimination of first-pass hepatic extraction. Portal venous drainage typically results in a more normal pattern of fasting and meal-stimulated insulin concentrations, with similar glucose control. Although insulin levels are elevated by systemic venous drainage, blood glucose homeostasis appears to be unaffected, demonstrating normal glucose utilization and hepatic glucose production. Whole pancreatic transplantation is also an effective treatment for patients who had a long history of severe, symptomatic hypoglycemia. The normal glucagon response to hypoglycemia is restored and hypoglycemic episodes are uncommon. Whole pancreas transplantation has been shown to be effective in providing recipients with long-term normal glycemic control off insulin (10 years or more). Reduced hemoglobin A1c levels are maintained and patients demonstrate fasting

blood glucose and glycemic control in response to a meal or glucose challenge similar to those of the non-diabetic population[9,24].

Secondary complications of IDDM

The microvascular, neurologic and macrovascular diseases associated with IDDM has been attributed to long-term poor glycemic control. Whereas the Diabetes Control and Complications Research Group reported that improved glucose control through intensive insulin therapy effectively delayed the onset, or slowed the progression of diabetic retinopathy, nephropathy and neuropathy, the risk of severe hypoglycemia was significant and only a small percentage of patients could sustain the required improvement in metabolic control. Whole pancreas transplantation has now been performed over a long enough period of time to allow study of the effect of sustained normal glycemic control in patients with IDDM.

Diabetic nephropathy

Whole pancreas transplantation does prevent de-novo diabetic changes, which would otherwise occur in a diabetic recipient of a kidney transplant[25]. There is also evidence that long-term successful pancreas transplantation may improve pre-existing histological changes secondary to diabetes in the native kidneys, although the effect is only observed after 5 or more years[26]. Whether native renal function benefits from PTA is uncertain, as the nephrotoxic effect of calcineurin inhibitor based immunosuppression therapy must be considered. Registry data has identified that from 2% to 8% of PTA recipients develop ESRF and require a kidney transplant by one year[9,27]. A recent report of case matched PTA with diabetic controls found however that although native renal function decreased significantly after PTA in patients with decreased creatinine clearance (CrCl $\leqslant$ 70 mL/min) at the time of transplantation, it was well tolerated among patients with a CrCl $\geqslant$ 70 mL/min[28]. Another study also found evidence for improvement of renal function after pancreas transplantation, documented by reduction of urinary excretion of protein with stable creatinine concentration and CrCl[29].

Diabetic retinopathy

The diabetic population undergoing pancreas transplantation typically has already developed some degree of retinal pathology and most have received laser therapy. Advanced retinal change does not seem to benefit from pancreatic transplantation as the damage has already occurred. Initial studies that examined the short-term effect of pancreas transplantation on diabetic retinopathy were unable to demonstrate any positive effect of corrected blood glucose control when compared to diabetic recipients of a kidney alone or SPK with a failed pancreas graft[30]. Studies which followed successful pancreas transplants for 5 or more years however, do show a benefit to the recipient with mild to moderate disease, with stabilization of established retinopathy, delay in the progression of new disease, improvement in visual acuity and a reduction in the use of laser therapy[9,31].

Diabetic neuropathy

Polyneuropathy is a common complication of both IDDM and ESRF and advanced motor, sensory and autonomic neuropathies are frequently seen in patients undergoing whole pancreas transplantation. Improvement of both motor and sensory neuropathies symptoms will occur following kidney transplantation alone, however correction of uremia secondary to diabetic nephropathy by kidney transplantation does not halt the progression of the underlying diabetic neuropathic process. Diabetic patients studied following pancreas transplantation with return to a normoglycemic state do show a significant early improvement in sensory and motor nerve conduction studies that continue to improve over time. However clinical neurological examination and testing for autonomic nerve dysfunction demonstrated little improvement, even when followed over a longer period of time[32-35].

Micro- and macrovascular disease

Diabetic microangiopathy, the result of chronic hyperglycemia and subsequent metabolic disturbances seen in IDDM, is the principle cause of many of the severe late complications of diabetes[36]. The progression of microvascular disease-related problems (e.g., nephropathy, retinopathy neuropathy) is reduced when tight glucose control has been obtained, either through intensive insulin therapy or following successful whole pancreas transplantation. Direct evidence for improvement of the microvasculature following pancreas transplantation can also be demonstrated. Skin blood flow characteristics (as measured by laser Doppler), a measure of the degree of microcirculation impairment, have been shown to improve (but not normalize) following pancreas transplantation when compared to non-diabetic controls[37]. The calcineurin-inhibitors, Cyclosporine and Tacrolimus, in addition to being nephrotoxic, have been shown to produce microangiopathy following transplantation and their use may negate any benefit a diabetic recipient might obtain from tight glucose control[38,39].

There is evidence that whole pancreas transplantation may reduce the risk of macrovascular disease. Carotid intima media thickness (determined by carotid ultrasound), a measure shown to correlate with the likelihood of cardiovascular events in IDDM (coronary artery disease, atherosclerotic vascular disease, mortality), is reduced following whole pancreas transplantation. The reduction of the carotid intima media thickness occurs early following transplantation and is independent of other causative factors such as smoking, age, serum lipid concentration and failure of a kidney transplant[40]. However, the typical recipient of a pancreas transplant has had long-standing IDDM and frequently has established vascular intimal disease and plaque formation and clinically significant vascular disease that may progress following transplantation[41].

Quality of life

Patients who have received a whole pancreas transplant consistently report an improvement in their quality of life (QOL), although pancreas transplantation is a complex

surgical procedure, requires life-long immunosuppression and careful follow-up, and is associated with a significant incidence of complications, including re-hospitalization. The improvement in QOL is maintained unless the pancreas recipient experienced graft loss. For patients with IDDM who are in ESRF, a significant improvement in their health may be expected following either correction of uremia or elimination of their diabetic state. In a prospective, longitudinal study of patients undergoing either SPK or kidney transplant alone (KTA), Gross *et al* found that the addition of a pancreas transplant increased the measure of QOL beyond the improvement seen with KTA and the pancreas recipients reported greater improvement in areas that are diabetes-specific[9,42-44].

Pancreatic islet transplantation

As discussed above, the Diabetes Control and Complications Trial Research Group reported that improved glycemic control through intensive insulin therapy delays the onset and slows the progression of diabetic complications. Improved glycemic control however, was hard to sustain and associated with intense insulin therapy was a significant increase in severe hypoglycemic episodes. Whole pancreas transplantation is capable of producing a sustained, euglycemic state, reducing the incidences of hypoglycemia and offering the possible benefit of reducing microvascular, macrovascular and neurologic complications. Pancreas transplantation however, is a major, complex surgical procedure associated with significant risk and cost that may limit its general acceptability, especially when a potential diabetic recipient has little evidence of renal impairment and does not need a kidney transplant.

Within the past 20 years, pancreatic islet transplantation has become a clinical reality and an option in the treatment of IDDM. Islet transplantation has a distinct advantage over whole pancreas transplantation in regards to reduced peri-procedure morbidity. The procedure avoids major surgery and the risk of associated post-operative complications, re-laparotomy and acute (vascularized) graft loss. Islet transplantation, with its ability to be cultured for a period of time prior to transplantation, also offers the future possibility of reducing the immunogenicity (both allo and auto) of the tissue such that little or no immunosuppression will be required.

Early efforts to treat IDDM patients with pancreatic islet transplantation were mostly unsuccessful. Although the first human pancreatic islet allografts were performed in 1974[45], it wasn't until 1991 that a pancreatic islet transplant recipient achieved sustained euglycemia off insulin (for 1 year)[46]. In 2000, the Edmonton group reported 7 consecutive islet transplant recipients achieving insulin independence. All recipients received islets from 2 pancreas donors (one received islets from 4 donors), and were maintained on a glucocorticoid-free immunosuppression protocol using Sirolimus and low-dose Tacrolimus[13]. The success of the Edmonton program has led to a general acceptance that islet transplantation is a clinically feasible therapy, which may be considered for the treatment of patients with IDDM, especially when accompanied by severe hypoglycemia. Since the report of success from Edmonton interest has grown in islet transplantation and now more than 40 centers in North America and many more worldwide are performing this procedure[47].

Patient selection

Pancreatic islet transplant, in general, has been restricted to patients with IDDM who suffer from hypoglycemic unawareness or metabolic instability, or have early evidence of secondary complications due to their diabetes. The patients require long-term, calcineurin-based immunosuppression and thus are subjected to the risks of these agents, such as nephrotoxicity, infection and malignancy. The patient may also become sensitized due to their alloimmune response to the transplant, potentially interfering with subsequent transplantation. Patients with evidence of significant diabetic renal impairment are excluded from islet transplantation until they either require or have undergone a kidney transplant. To improve the likelihood of attaining euglycemia off insulin, most transplant programs and clinical trials will restrict islet transplantation therapy to patients weighting less than 70 kg, a body mass index (BMI) < 27 and not requiring an excessive amount of daily insulin for glycemic control[47-51].

PANCREATIC ISLET TRANSPLANT PROCEDURE

Islet isolation and culture

One of the key elements attributed to the success of the Edmonton program (Edmonton Protocol) was the need to transplant high-quality, purified islets in sufficient numbers. This usually requires isolation of islets from two or more whole pancreata. Refinement of the islet isolation process, with the standardizing of pancreas digestion (the universal use of controlled pancreatic duct perfusion with collagenase and the Ricordi digestion chamber) and use of the COBE cell processor (continuous gradient purification system) for islet purification from exocrine tissue now allows many transplant centers a source of high-quality islets[52-54]. Although some centers transplant the isolated, purified pancreatic islets immediately, other centers maintained the islets in culture for a short period (up to 48 h) prior to transplantation. Holding islets in culture for a short period does not seem to have a detrimental affect on their viability and function and allows the transplant center the option of pre-conditioning the islet tissue (to reduce immunogenicity or improve post-transplant viability), or initiate immunosuppression treatment of the recipient prior to the transplant[55-57].

In the islet recipient, access to the portal vein is obtained by either percutaneous transhepatic portal venous catheterization or mini-laparotomy. The pancreatic islets are suspended in an albumin solution and infused by gravity, along with heparin through the portal vein to embolize in the liver. Prophylactic anticoagulation is continued for several days to reduce the likelihood of an instant blood-mediated inflammatory reaction (IBMIR) with subsequent clot formation and inflammatory

response that has been shown to lead to islet damage[58-60]. Islet recipients are routinely given exogenous insulin to maintain blood glucose levels in a physiologic range as hyperglycemia in the early post-transplant period has been shown to be detrimental to islet function and may interfere with islet engraftment[55,56,61].

Procedural complications

Pancreatic islet transplantation is a less invasive alternative to whole pancreas transplantation and has been shown to be associated with a much lower risk of serious complications. The majority of serious adverse events reported in 2006 by the Collaborative Islet Transplant Registry (CITR) were related to the infusion procedure: bleeding, hematoma and portal vein thrombosis (41.9%)[47]. Newer catheters and radiologic techniques for sealing the intra-hepatic tract used for portal vein infusion of the islets has resulted in a reduction in the incidence of post procedural bleeding[62]. Increased purity of the islet preparation with a subsequent decreased total islet volume infused into the liver may also reduce the likelihood of portal pressure elevation, a risk factor that has been associated with bleeding, in particular, with a second or subsequent islet transplant. The routine use of anticoagulation has likely limited the incidence of portal vein thrombosis, however has been shown to be a factor in the rate of procedural bleeds. Following transplantation, liver transaminases typically are elevated; however routinely return to the normal range within 4 wk[50]. The long-term consequences of intra-hepatic islet infusion are not yet known. The Edmonton group has reported changes consistent with fatty liver in 8 of their first 36 patients on magnetic resonance imaging following transplant.

Immunosuppression

Since 1999, in the US the majority of islet transplant programs (> 90%) use Sirolimus and Tacrolimus in combination as maintenance immunosuppression (Edmonton Protocol). All programs used one or more induction immunosuppression agents at the time of the first islet infusion, the most common being a non-depleting monoclonal anti-CD25 antibody. Complications related to immunosuppression therapy were the second most common severe event reported by CITR (29.6%). Whereas some studies have reported that islet transplant recipients may demonstrate evidence of deterioration of renal function (immunosuppression related) especially where creatinine clearance is already significantly impaired, others have reported no deleterious renal effect following islet transplant[14,47,51].

OUTCOMES OF PANCREATIC ISLET TRANSPLANTATION

Collaborative islet transplant registry

In a survey of all North American transplant programs by CITR, 31 active programs reported 593 islet infusion procedures in 319 recipients during the period 1999-2005[47]. CITR has information on 225 of the 319 allograft recipients (71%) and 425 of the 593 infusion procedures (72%) from 23 participating centers. Sixty-four of the recipients (28.4%) received one islet infusion, 122 (54%) received two, 38 (17%) received three, and one received a total of four islet infusions. Of the 225 recipients, 203 (89%) received an islet transplant alone, while 22 recipients (10%) had previously received a kidney transplant prior to the islet transplant. Insulin independence (off insulin for 14 days or more) was achieved by 69.7% of islet recipients at some point following their last transplant (within two years). Considering all participants, 46.6% remained insulin independent for at least one year following their last transplant and 33.3% were insulin independent at 2 years. Patients who had achieved insulin independence at any point, at one year had a basal C-peptide level (1.1 ng/mL, SD 0.65), and hemoglobin A1c (6%, SD 0.8) in the normal (or near normal) range. Severe hypoglycemic events were shown to be dramatically deceased following the first islet infusion. Greater than 85% of recipients had one or more severe hypoglycemic event prior to transplant, compared to less than 5% in the first year following the transplant.

International trial of the edmonton protocol for islet transplantation

In 2006, a study organized by the Immune Tolerance Network (initiated by the National Institutes of Health) among six North American and three European transplant centers to assess the feasibility and reproducibility of the Edmonton Protocol reported their results[14]. Each center was confined to use the islet isolation technique and immunosuppression protocol as described by the Edmonton group. In the period 2001-2003, 36 patients underwent 77 islet infusion procedures. Eleven of the recipients (31%) received one islet infusion, 9 (25%) received two and 16 (44%) received three infusions. Insulin independence was achieved by 21 patients (58%) at some point, 16 patients (44%) remained insulin independent for one year and 5 (14%) remained insulin-independent at 2 years following their last transplant (35 patients evaluated at 2 years). Although most patients had returned to requiring insulin by two years, C-peptide remained detectable in 70%, demonstrating persistence of islet function. Average hemoglobin A1c levels were in shown to be in the normal range for patients who remained insulin-independent at 2 years, and only slightly elevated above normal when partial graft function was demonstrated. All patients with residual islet function were completely protected from severe hypoglycemic episodes.

Secondary complications of IDDM

Successful islet transplantation, with correction of glycemic control has only been a clinical reality for a short period of time and there has been little published to-date on the effect of islet transplantation on the secondary complications (microvascular, neurologic and macrovascular diseases) associated with IDDM. Assessment of the long-term safety and effectiveness of islet transplantation for the treatment of IDDM will require the future report of more centers with longer periods of follow-up.

CONCLUSION

Both whole pancreas transplantation and pancreatic islet transplantation have been shown to be successful at creating a euglycemic state in a patient with IDDM with preprandial and postprandial blood glucose concentrations and hemoglobin A1c levels comparable to those in the non-diabetic population. Both forms of transplants are also effective at eliminating the occurrence of significant hypoglycemic events (even with only partial islet function evident). Whole pancreas transplantation has also been shown to be effective at maintaining a euglycemic state over a sustained period of time, and thus provides an opportunity for a recipient to benefit from improvement of their blood glucose control (halt or reverse secondary complications of IDDM). Islet transplantation is attractive as a less invasive alternative to whole pancreas transplantation and offers the future promise of immunosuppression-free transplantation through pre-transplant culture. Although recent advances have led to an increased rate of obtaining insulin-independence following islet transplantation, further developments are needed to improve the long-term viability and function of the graft to maintain improved glucose control over time.

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