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Australia and New Zealand Horizon Scanning Network

ANZHSN

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AND THE GOVERNMENT OF NEW ZEALAND

Horizon Scanning Technology Prioritising Summary

Allogeneic pancreatic islet cell transplantation

August 2008



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**Australian
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Procedures -
Surgical**



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College of Surgeons**

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PRIORITISING SUMMARY

REGISTER ID **S000082**

NAME OF TECHNOLOGY **ALLOGENEIC PANCREATIC ISLET CELL TRANSPLANTATION.**

PURPOSE AND TARGET GROUP **TO ACHIEVE INSULIN-INDEPENDENCE IN PATIENTS WITH TYPE 1 DIABETES MELLITUS.**

STAGE OF DEVELOPMENT (IN AUSTRALIA)

- | | |
|---|--|
| <input type="checkbox"/> Yet to emerge
<input type="checkbox"/> Experimental
<input checked="" type="checkbox"/> Investigational
<input type="checkbox"/> Nearly established | <input type="checkbox"/> Established
<input type="checkbox"/> Established <i>but</i> changed indication or modification of technique
<input type="checkbox"/> Should be taken out of use |
|---|--|

AUSTRALIAN THERAPEUTIC GOODS ADMINISTRATION APPROVAL

- | | |
|---|-----------------------|
| <input type="checkbox"/> Yes
<input type="checkbox"/> No
<input checked="" type="checkbox"/> Not applicable | ARTG number NA |
|---|-----------------------|

INTERNATIONAL UTILISATION

COUNTRY	LEVEL OF USE		
	Trials Underway or Completed	Limited Use	Widely Diffused
Australia	✓		
Canada		✓	
China	✓		
Germany		✓	
Italy		✓	
Japan	✓		
Switzerland	✓		
UK		✓	
USA		✓	

IMPACT SUMMARY

Allogeneic pancreatic islet cell transplantation is a potential alternative to insulin therapy, whole-pancreas transplantation and diet regulation, for the management of type 1 diabetes mellitus. This technology is currently in the investigational stage in Australia.

BACKGROUND

Type 1 diabetes mellitus is a chronic metabolic disorder caused by an absolute or relative deficiency of insulin, an anabolic hormone normally produced by the beta cells of the islets of Langerhans in the pancreas (Lamb 2007). It is understood type 1 diabetes results from an autoimmune-mediated destruction of these insulin-secreting beta cells (Bretzel et al 2007). When insulin levels in the blood are low the normal use and storage of glucose is inhibited, causing an increase in glucose levels, known as hyperglycaemia (Lamb 2007). Because the kidneys cannot reabsorb the excess glucose, glycosuria, osmotic diuresis, thirst and dehydration result (Lamb 2008). Increased fat and protein breakdown leads to ketone production and weight loss (Lamb 2008). Without insulin therapy patients with type 1 diabetes are likely to develop diabetic ketoacidosis, and eventually die (National Institute for Health and Clinical Excellence (NICE) 2007). Even with medical intervention, patients with type 1 diabetes have an increased risk of developing other long-term health problems such as, heart disease, blindness, kidney failure, foot ulcers, peripheral vascular disease and autonomic neuropathy (NICE 2007). Patients with type 1 diabetes are also at risk of hypoglycaemia, where the level of glucose in the blood becomes very low, during such episodes patients are required to take glucose (in the form of an injection or sugary sweet), if untreated the patient may become unconscious, have seizures, suffer injuries or die (NICE 2007).

For patients with type 1 diabetes mellitus, replacement of their defective islets of Langerhans by whole-pancreas transplantation or isolated islet cell transplantation appears to be their only means of achieving insulin-independence, constant normal glycaemia and avoidance of hypoglycaemic episodes (Bretzel et al 2007). Presently, simultaneous pancreas and kidney transplantation are considered the standard of care for selected patients with type 1 diabetes and end stage renal failure (Bretzel et al 2007). In this group, insulin-independence was seen in greater than 85% of recipients one year after transplant; however, pancreas transplantation is associated with significant perioperative morbidity and mortality (Bretzel et al 2007). Because isolated islet cell transplantation is a minimally invasive procedure, it can potentially reduce this risk, as well as reduce the intensity of immunosuppression required postoperatively.

Allogeneic pancreatic islet cell transplantation involves the removal of the pancreas from one or more dead or brain dead human donors so that their islet cells can be isolated for transplantation into a diabetic recipient (Bretzel et al 2007). These cells are then infused into the liver via a catheter inserted into the portal vein. This can occur either percutaneously (under fluoroscopic guidance) or laparoscopically via a tributary such as the mesenteric vein (NICE 2007). The patient remains under local anaesthetic and is given antibiotics, immunosuppressants and insulin throughout the procedure (NICE 2007). Multiple islet infusions may be required before the pancreas can produce adequate

amounts of insulin on its own — typically two islet cell infusions are sufficient in achieving this (Ryan et al 2005).

In September 2001, the Collaborative Islet Transplantation Registry (CITR) was founded. The aim of the CITR is to compile and analyse data from all transplant centres in the US, Canada and some European and Australian Centres, to accelerate the identification of critical risks associated with the procedure and key determinants of its success, as well as to inform refinement to the protocol (CITR 2008).

CLINICAL NEED AND BURDEN OF DISEASE

In 2004–05, 3.5% of the Australian population suffered from diabetes, which was close to 700,000 individuals (Australian Bureau of Statistics (ABS) 2008a). Of these, 13% had type 1 diabetes — or 0.5% of the Australian population (ABS 2008a). The proportion of Australians with type 1 diabetes mellitus remained constant from 1995–2005 (ABS 2008a).

In a National Health Survey regarding the self-assessed health status of people with and without diabetes, twice as many people aged ≥ 15 years with diabetes (both type 1 and 2) described their health as fair or poor (40%), compared with people of the same age without diabetes (15%) (ABS 2008b). Diabetics ≥ 18 years were also more likely to have high levels of psychological distress (8%), than non-diabetics (4%) (ABS 2008b). People with diabetes were found to have a higher risk of suffering several other health complications, particularly in those aged ≥ 45 years (ABS 2008b). These included hypertension, heart, stroke or vascular conditions, elevated cholesterol, urinary system disease or non-circulatory fluid retention, nerve or blood vessel damage (leading to amputation) and sight problems (ABS 2008b). Sight problems were apparent in 15% of people aged ≥ 45 years with diabetes — 33% had type 1 diabetes (ABS 2008b). Diabetics were 2.3 times more likely to develop glaucoma, 1.6 times more likely to develop cataracts and 1.7 times more likely to develop partial or complete blindness (ABS 2008b). Approximately 30% of people with type 1 diabetes will eventually suffer kidney disease (ABS 2008b).

A 2003 Survey of Disability, Aging and Carers found 50% of people with diabetes had a disability, 24% of which named diabetes as the main condition causing their disability (ABS 2008b). Of the 150,000 diabetics aged 15–64 years with concurrent disability 45% were unable to work, and 82% reported some restriction to their employment due to their condition (ABS 2008b). In 2004, diabetes was the underlying cause or associated cause of 11,700 deaths in Australia (ABS 2008b).

From 2004–05, administration data shows 67,700 hospital separations due to diabetes, accounting for 1.0% of all hospitalisations (ABS 2008b). From 2000–01 to 2004–05, the number of hospital separations had increased by approximately 1,500 cases (ABS 2008b).

DIFFUSION

Investigations into the effect of transplanting islets of Langerhans into human diabetic patients were first noted in 1893, with poor results (Bretzel et al 2007). It was in 1999

that a new protocol for the transplantation of islet cells was implemented in Edmonton, Canada (Bretzel et al 2007). One year later, the protocol was successfully used to reverse diabetes in seven consecutive patients (Bretzel et al 2007). From this success came a significant increase in clinical islet cell transplant trials, with an estimated 652 type 1 diabetics treated across 47 institutions from 1999–2005 (Bretzel et al 2007).

Trials have been conducted throughout Europe, Asia, Canada, the UK and US. Since the Edmonton experience further refinements to the protocol have taken place, thus increasing the worldwide use of the technique. Islet cell transplantation in Australia is in the investigational stage, with research into the identification of factors that cause graft damage and the development of safer immunosuppressant regimes currently being conducted (Westmead Millennium Institute for Medical Research 2008).

The 2007 CITR annual report described islet allograft transplantation activity from 1999–2006. Data from 31 North American medical centres and one European centre was pooled to find there were 292 islet cell recipients, 579 individual transplantation procedures and 634 islet cell donors during this time (CITR 2008). However, until all participating institutions report every islet transplantation event the data obtained from CITR will be affected by bias, particularly selection bias.

COMPARATORS

Management of insulin and glucose levels are imperative for the survival of patients with type 1 diabetes. The most common mechanism of controlling diabetes is the use of multiple insulin injections, which are usually self-administered at fixed times of the day (NICE 2007). Insulin can also be delivered through subcutaneous infusion facilitated by a pump permanently attached to the patient, where a varied dose of fast-acting insulin is administered continuously throughout the day and night at a rate appropriate for the patient's needs (NICE 2007). In addition to insulin therapy, patients may be advised to make particular lifestyle changes such as diet and weight-loss. Dietary management is important in avoiding hyper- or hypo- glycaemia following a meal, to prevent these events occurring patients should be aware of the implications of meal timing, size and composition (NICE 2007).

A direct comparator of islet cell transplantation is whole-pancreas transplantation, as both procedures aim to make the patient insulin-independent. Currently, whole-organ kidney and pancreas transplantation are the gold standard in treating patients with diabetes and end stage kidney disease (Bretzel et al 2007).

SAFETY AND EFFECTIVENESS ISSUES

Three studies were identified for inclusion in this summary. One nonrandomised comparative study comparing the quality of life outcomes of type 1 diabetics undergoing islet transplantation with type 1 diabetics undergoing conventional treatments (Toso et al 2007) and two case-series reporting on the outcomes of islet transplantation in different patient groups (Ryan et al 2005; Close et al 2007).

The case-series by Ryan et al (2005) assessed five-year follow-up after clinical islet transplantation using the Edmonton protocol. Sixty-five patients with type 1 diabetes mellitus underwent islet cell transplantation, at a single institution. Indications for treatment included at least one of the following, problematic hypoglycaemia, defined as recurrent hypoglycaemic episodes generally associated with loss of consciousness and a Hypoglycaemic score (HYPO score) $\geq 1,047$, or labile diabetes, characterised by large variations in blood glucose which interfere with the patient's quality of life and is defined by a lability score (LI) $\geq 433 \text{ mmol/l}^2 \cdot \text{h}^{-1} \cdot \text{week}^{-1}$. The mean age of the 28 male patients and 37 female patients was 42.9 ± 1.2 years and the mean duration of diabetes was 27.1 ± 1.3 years. Their median weight was 68.5 kg (interquartile [IQ] range 62.8–78.1) and the median units of insulin administered per day, at baseline, was 45 (IQ range 35–55).

Each patient received at least one islet cell transplantation, 52 patients received two and 11 received three. A total of 128 transplantations took place, the majority of which were performed percutaneously, with only four through mini-laparotomy. Of these procedures, most were facilitated by one donor, with 12 recipients requiring two donors. Daclizumab, sirolimus and tacrolimus were given to suppress the immune system from rejecting the transplanted cells, and prophylactic antibiotics (sulfamethoxazole/trimethoprim and ganciclovir) were administered for up to six months posttreatment (Ryan et al 2005).

Patients were seen every 1- to 6- months throughout the five year follow-up. Treatment ceased when patients were either insulin-independent, or if they had received $> 15,000$ islet equivalents (IE) and had not reached insulin-independence. Insulin-independence occurred when the patient had not required exogenous insulin for four weeks and did not receive $> two$ readings of $> 10.0 \text{ mmol/l}$ on their capillary glucose testing (Ryan et al 2005).

The case-series by Close et al (2007) analysed the success of islet cell transplantation from data obtained from the CITR second annual report (2005). One hundred and thirty-eight type 1 diabetic recipients were registered on the CITR at that time and were eligible for inclusion. Of these, 118 were islet transplant-alone recipients, 19 had previous kidney transplantations and one was an autograft transplant recipient. The median age of islet transplant-alone recipients was 41.6 years (range 23.1–64.4) and their median duration of diabetes was 29 years (range 4–50). Of the entire sample, 47 were male and 91 female, with a median weight of 65 kg (range 47–97) and median BMI of 23.1 kg/m^2 (range 18.8–31.6). On average, 36.6 units (standard deviation (SD) 12.9) of insulin were required per day by the patients before receiving treatment. The mean duration of insulin therapy was 15.1 years (SD 11.1). The most common immunosuppressant therapy used consisted of daclizumab, sirolimus and tacrolimus, although other suppressant variations were used on a case-by-case basis.

The nonrandomised comparative study by Toso et al (2007) investigated the health-related quality of life and fear of hypoglycaemia in patients following islet transplantation. Ninety-nine patients with type 1 diabetes undergoing islet cell transplantation were compared with 166 control patients, also with type 1 diabetes, undergoing normal insulin treatment. Clinical outcomes were measured using two

questionnaires; the Health Utilities Index Mark 2 (HUI2) and the Hypoglycaemia Fear Survey (HFS). HUI2 assessed the overall quality of life of patients in regards to six attributes (sensation, mobility, emotion, cognition, self-care and pain/discomfort). HFS questioned patient concerns with hypoglycaemia and what they have done to prevent such episodes in the past.

There were 44 male patients and 55 female patients in the treatment group, with a mean age of 44.3 ± 9.6 years and mean duration of diabetes of 28.4 ± 10.7 years. Patients in the control group were significantly matched in regards to sex (70 male, 96 female) and age (42 ± 12.3 years; $P > 0.05$). The duration of diabetes in the control group (23.8 ± 12.6 years) was significantly shorter than in the treatment group ($P < 0.05$). HUI2 results were similar between the groups at baseline; however, HFS results were not, with significantly more fear in patients awaiting islet transplantation ($P < 0.000001$) (Toso et al 2007).

Safety

In the study by Ryan et al (2005), 15 patients experienced major bleeding following percutaneous islet infusion. Of these, seven patients required transfusions and two required laparotomy. Five patients had thrombus in segmental branches of the portal vein, which were completely resolved with anticoagulation. Two patients had their gall bladder punctured, which was treated conservatively. Mean portal vein pressure increased significantly from baseline to posttreatment ($P < 0.001$). Liver transaminases increased by > 2.5 times the upper limit of normal in 55% of patients and by > 5 times the upper limit of normal in 23% of patients — these abnormalities resolved within four weeks. Fatty liver was seen in 8 patients (22%).

Immunosuppressant complications included, mouth ulcers in 89% of patients, diarrhoea in 60%, acne in 52%, oedema in 43% and ovarian cysts in premenopausal women. Weight-loss was common, as weight varied significantly from baseline to one year ($P < 0.001$). Three patients had pneumonia, one of which was thought to be of fungal origin. One other patient had two small foci of papillary carcinoma of the thyroid. Throughout follow-up, diabetic complications were also common. Four patients (9%) experienced deterioration of an eye condition requiring photocoagulation or vitrectomy within five months of treatment. From baseline to posttreatment, the number of patients requiring medication for hypertension and cholesterol increased. One patient died suddenly 22.5 months posttreatment of an accidental cause, with functioning islet cells (Ryan et al 2005).

In the study by Close et al (2007), during the first year of follow-up, at least one adverse event was recorded in 61 islet transplant-alone patients (74%). The total number of adverse events was 235; 34% related to immunosuppressant regimen and 14.5% related to infusion procedure. During the same time, serious adverse events were seen in 30 patients (36%; 52 individual events); 28.8% related to immunosuppression and 23.1% related to procedure. Among the 138 participants, 77 serious adverse events were reported overall; of these 17 (22%) were life-threatening, 45 (58%) required hospitalisation and 73 (95%) resolved completely. Commonly, serious adverse events

were related to gastrointestinal disorders, blood and lymphatic system disorders and infections or infestations.

Toso et al (2007) reported no safety data.

Effectiveness

Forty-four patients (68%) were insulin-independent by the end of follow-up. Five patients were insulin-independent after one islet infusion, 33 were insulin-independent after two infusions and 6 were insulin-independent after three infusions. A further three patients who had received in excess of 16,000 IE/kg remained insulin-dependent. Despite persistent graft survival a significant number of recipients resumed insulin therapy to maintain control of their blood glucose. There was not a significant difference seen between the numbers of infusions required in regards to the persistence of insulin-independence. Insulin-independence occurred for \geq one month in 44 patients (94%), the median duration was 15 months. The median duration for graft function, indicated by C-peptide secretion was 25.2 months. There was a relationship seen between graft survival and the quantities of insulin required per day pretreatment. Patients who lost all graft function (no detectable C-peptide) generally required more insulin at baseline, than those with consistent graft function and C-peptide secretion ($P<0.001$). Blood glucose, measured by glycosylated haemoglobin (HbA_{1c}) increased once graft survival was lost and was poorly controlled in the 9% of patients in which this occurred. HbA_{1c} was well controlled in patients with insulin-independence (6.4%) and those who required insulin but were C-peptide positive (6.7%). HYPO score and LI showed improvement after transplantation, in the patients who reverted back to insulin usage some episodes of hypoglycaemia and lability occurred; however, these scores still remained improved from baseline for up to four years.

In the study by Close et al (2007), 112 islet transplant-alone recipients completed at least one year follow-up, 55 (49.1%) of which were insulin-independent. Thirty-nine patients were insulin-dependent at this time. A total of 15 patients (13.4%) had complete graft failure. Overall, 67% of patients at 6 months follow-up were insulin-independent; however, this decreased to 58% by 12 months follow-up. In the patients requiring insulin at 6 months there was a marked reduction (58% [range 4.8–83.3]) in the daily amount required, compared with baseline. This reduction increased to 69% (range 16.7–92.4) by 12 months follow-up. A large reduction in hypoglycaemic episodes was seen in the first year following transplantation. Over 82% of islet transplant-alone patients experienced hypoglycaemia in the year leading up to their treatment; whereas, hypoglycaemia only occurred in 2.5% of patients at 30 days' follow-up and in a further 2% up to 12 months follow-up.

In the study by Toso et al (2007), 69/89 patients (76%) were insulin-independent upon completion of islet cell transplantation. At one month follow-up, patients receiving islet transplantation had significantly lower overall HUI2 scores (0.75 ± 0.17) than at baseline ($P<0.05$), eventually results returned to baseline levels (up until 36 months; $P>0.05$). In breaking down HUI2 scores by attributes, patients in the treatment group experienced reduced pain after the first infusion (0.83 ± 0.24), compared with baseline (0.92 ± 0.11),

which remained at one month ($P<0.01$), but returned to baseline levels thereafter. Emotion was also significantly improved for the treatment group between the first and second infusions, compared with baseline (0.93 ± 0.11 versus 0.89 ± 0.12 ; $P<0.01$); however, this value also returned to baseline equivalence thereafter. The remaining attributes were stable throughout. HFS reduced significantly to 40.2 ± 18.7 after the first infusion from 53.1 ± 13.8 at baseline ($P<0.00001$), and even further by the completion of full islet transfer ($P\leq 0.01$). HFS remained low in this patient group through to 24 months, and increased again at 36 months. A relationship was seen between HFS and pretreatment HYPO score ($r=0.47$, $P=0.010$), LI ($r=0.56$, $P=0.0007$) and insulin requirement ($r=0.69$, $P=0.000002$). At one year follow-up, insulin-independent patients had less fear of hypoglycaemia than those patients on insulin (7.8 ± 8.4 versus 23.6 ± 18.5 ; $P<0.0001$).

COST IMPACT

In 2000–01, health system expenditure on diabetes was estimated at \$784 million, or 1.7% of allocatable recurrent health expenditure (Australian Institute of Health and Welfare (AIHW) 2008). This is equivalent to \$1,469 per known case of diabetes, or \$42 per Australian (AIHW 2008). The largest costs were worn by hospital services (\$231 million) and prescription pharmaceuticals (\$221 million) (ABS 2008b).

No literature was found regarding the cost of whole-pancreas transplantation versus isolated islet cell transplantation; however, it is likely that whole-organ transplantation would be more expensive because it is a more invasive procedure, with a longer recovery period and greater risk of complications. The New South Wales health department estimated the inpatient costing of pancreas transplantation at \$52,000 (NSW Health 2008).

ETHICAL, CULTURAL OR RELIGIOUS CONSIDERATIONS

No issues were identified from the retrieved material.

OTHER ISSUES

No issues were identified from the retrieved material.

SUMMARY OF FINDINGS

The three included studies do not provide sufficient evidence to determine the safety and effectiveness of allogeneic pancreatic islet cell transplantation for the treatment of type 1 diabetes mellitus, particularly owing to the lack of high quality evidence available, as well as the insufficiency of follow-up duration. The technology appears to be effective in a subset of patients in the short-term (one to two years) only, and the adverse events and serious adverse events associated with the technique are far too frequent as the procedure stands, these may be reduced by further refinements of the treatment protocol.

HEALTHPACT ACTION

Due to the lack of long-term benefits of allogeneic pancreatic islet cell transplantation, further refinement of the technique is required. Considering the fact that high quality results will not be available for some time, it is recommended that allogeneic pancreatic islet cell transplantation be archived.

NUMBER OF STUDIES INCLUDED

Total number of studies	3
Level III-2 evidence	1
Level IV evidence	2

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SOURCES OF FURTHER INFORMATION

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SEARCH CRITERIA TO BE USED

Islets of Langerhans

Beta cells

Transplantation

Diabetes mellitus, type 1