Pancreatectomy is utilized in the treatment of patients with chronic pancreatitis. Autologous islet transplantation, performed in conjunction with pancreatectomy, is proposed for chronic pancreatitis patients. Allogeneic islet transplantation is proposed for selected patients with type 1 diabetes.

In autologous islet transplantation, during the pancreatectomy procedure, islet cells are isolated from the resected pancreas using enzymes, and a suspension of the cells is injected into the portal vein of the patient’s liver. Once implanted, the beta cells in these islets begin to make and release insulin. In the case of allogeneic islet cell transplantation, cells are harvested from the deceased donor’s pancreas, processed, and injected into the recipient’s portal vein. Up to 3 donor pancreas transplants may be required to achieve insulin independence. Allogeneic transplantation may be performed in the radiology department.

Chronic Pancreatitis

Primary risk factors for chronic pancreatitis include toxic-metabolic, idiopathic, genetic, autoimmune, recurrent and severe acute pancreatitis, or obstructive (the TIGAR-O classification system). Patients with chronic pancreatitis may experience intractable pain that can only be relieved with a total or near total pancreatectomy. However, the pain relief must be balanced against the certainty that the patient will be rendered an insulin-dependent diabetic. Autologous islet transplantation has been investigated as a technique to prevent this serious morbidity.

Type 1 Diabetes
Allogeneic islet transplantation has been used for type 1 diabetes to restore normoglycemia and, ultimately, reduce or eliminate the long-term complications of diabetes such as retinopathy, neuropathy, nephropathy, and cardiovascular disease. Islet transplantation potentially offers an alternative to whole-organ pancreas transplantation. However, a limitation of islet transplantation is that 2 or more donor organs are usually required for successful transplantation, although experimentation with single-donor transplantation is occurring. A pancreas that is rejected for whole-organ transplant is typically used for islet transplantation. Therefore, islet transplantation is recommended only for patients with frequent and severe metabolic complications who have consistently failed to achieve control with insulin-based management.

**Regulatory Status**

Islet cells are subject to regulation by the U.S. Food and Drug Administration (FDA), which classifies allogeneic islet cell transplantation as somatic cell therapy, requiring premarket approval. Islet cells also meet the definition of a drug under the federal Food, Drug, and Cosmetic Act. Clinical studies to determine safety and effectiveness outcomes of allogeneic islet transplantation must be conducted under FDA investigational new drug (IND) regulation. While at least 35 IND applications have been submitted to the FDA, no center has submitted a biologics license application.

**Policy**

Autologous pancreas islet transplantation may be considered **medically necessary** as an adjunct to a total or near total pancreatectomy in patients with chronic pancreatitis.

Allogeneic islet transplantation is considered **investigational** for the treatment of type 1 diabetes.

**Policy Guidelines**

CPT code 48160 explicitly describes autologous pancreas islet cell transplantation.

Effective October 1, 2004, there are 3 HCPCS codes specific to these procedures:

- G0341 Percutaneous islet cell transplant, includes portal vein catheterization and infusion
- G0342 Laparoscopy for islet cell transplant, includes portal vein catheterization and infusion
- G0343 Laparotomy for islet cell transplant, includes portal vein catheterization and infusion

Between 2006 and 2012, there were 3 category III CPT codes specific to these procedures:

- 0141T Pancreatic islet cell transplantation through portal vein, percutaneous
- 0142T Pancreatic islet cell transplantation through portal vein, open
Rationale

The policy was created in 2001 and was updated regularly with searches of the MEDLINE database. The most recent literature was for the April 2011 through April 2012. Following is a summary of the key literature to date on islet cell transplantation.

Chronic Pancreatitis

In 2012, Bramis and colleagues published a systematic review of studies on islet transplantation after total pancreatectomy in patients with chronic pancreatitis. (1) The investigators searched for studies reporting on patients who had been treated with total, subtotal or completion pancreatectomy followed by islet autotransplantation. Case series were included if they included more than 5 individuals and reported outcomes for consecutive patients. A total of 72 full-text articles were reviewed, and 5 studies were found to meet inclusion criteria. The postoperative insulin independence rate in the 5 studies ranged from 10% (mean follow-up=8 years) to 46% (mean follow-up=5 years). In the study with the longest follow-up, the insulin independence rate was 28% at 10 years. Two studies reported postoperative morphine use. In one study, patients reported a mean post-operative decrease in morphine use of 116 mg and in the other, a mean decrease of 55 mg of morphine was reported.

A second recent systematic review of studies on islet transplantation after pancreatectomy was published in 2011 by Dong and colleagues. (2) Studies were included regardless of design or sample size. After reviewing 84 studies, 15 observational studies were found to meet eligibility criteria. There were 11 studies of total pancreatectomy, 2 studies of partial pancreatectomy, and 2 studies that included both types of surgery. Sample sizes in individual studies ranged from 3 to 173 patients. Thirteen studies included patients with chronic pancreatitis, and 2 included patients with benign pancreatic tumors. The pooled 30-day mortality was 5% (95% confidence interval [CI]: 2 to 10%), and the cumulative mortality at 1 year (reported by 10 studies) was 4.9% (95% CI: 2.6 to 7.3%). In a pooled analysis of data from 14 studies, the rate of insulin dependence at last follow-up was 4.6 per 100 person years (95% CI: 1.53 to 7.62). The pooled rate of insulin independence at 1 year (5 studies) was 27% (95% CI: 21-33%) and at 2 years (3 studies) was 21% (95% CI: 16-27%).

Representative studies are described below:

A large single center series was reported by Sutherland and colleagues in 2012. (3) (This study was too recent to be included in the recent systematic reviews). The study included 409 patients with chronic pancreatitis who underwent total pancreatectomy and islet transplantation between February 1977 and September 2011. Fifty-three of 409 patients (13%) were children between the ages of 5 and 18 years. Actuarial survival post-surgery was 96% in adults and 98% in children after 1 year and 89% in adults and 98% in children after 5 years. A total of 15.9% of patients experienced surgical complications requiring reoperation during the initial admission. The most common reason for reoperation was bleeding, occurring in 9.5% of patients. At 3 years, 30% of patients were insulin-independent (25% of adults and 55% of children). A survey
of quality-of-life outcomes was initiated in October 2008; responses were available for 102 patients. At baseline, all 102 patients reported using narcotics for pain. At 12 months, the proportion of patients on narcotics decreased to 56% (n=32), and at 24 months, 41% of respondents (n=21) reported using narcotics.

In 2009, Garcea and colleagues reported outcomes (pain relief, insulin requirements, and glycemic control) in 85 consecutive patients who had total pancreatectomy with or without islet cell transplant. (4) Five patients were insulin-independent, and median 24-hour insulin requirements were significantly lower in the islet group (15.5 vs. 40 units, respectively) at 5 years’ postoperatively (p=0.001).

In 2008, Webb and colleagues reported on 46 patients who had total pancreatectomy with immediate islet auto transplant. Twelve had periods of insulin independence for a median of 16.5 months (range, 2–63 months), and 5 remain insulin-independent. (5) Insulin requirements increased over the 10-year follow-up, as have HgA1c levels; however, all patients tested were C-peptide positive at their most recent assessment, and high fasting and stimulated C-peptide positive values recorded at 10 years after transplantation suggest significant graft function in the long term.

Type 1 Diabetes

In April 2004, TEC completed an evidence report on islet cell transplantation in type 1 diabetes in its capacity as an Evidence-based Practice Center for the Agency for Healthcare Research and Quality (AHRQ). (6) The evidence report found that published data on clinical outcomes of islet-alone transplantation were limited by small patient numbers, few transplant centers, short duration of follow-up, and lack of standardized methods of reporting clinical outcomes. Clinical outcomes from available data can be summarized as follows:

- The published technical success rate for islet alone transplantation at the time of the TEC Assessment was high: 94% of transplanted patients achieved insulin independence over the 3-month post-transplant period.
- The published insulin independence rate at 1 year was 76% (37 patients; 3 centers). The more recent abstracts reported rates of 50–90% (104 patients; 4 centers).
- The 2-year insulin-independence rate was approximately 64% based on published and supplemental data from 1 center (15 patients with 2 or more years of follow-up; 48 total).
- In all insulin-independent patients, hypoglycemic episodes were completely abated and mean HbA1c decreased from greater than 7% to less than 6.5%.
- Patients who did not achieve or who lost insulin independence tended to use 25–75% of pre-transplant insulin doses, continued to produce C-peptide, and were free of hypoglycemic episodes.
- Eighty-three percent of 23 patients from 2 institutions were euglycemic at 1 year, without hypoglycemic episodes, and free of or receiving reduced insulin.

Rare, serious adverse events have occurred in patients given islet transplants; recent procedure modifications reportedly minimize risks of these adverse events. No procedure-related deaths, cytomegalovirus (CMV) infection, or post-transplantation lymphoproliferative disease (PTL) have been reported for islet-alone transplantation.
The 2008 update from the Collaborative Islet Transplant Registry, which collects and monitors data on allogeneic islet transplantation in North America, Europe, and Australia, reported that as of April 2008, their registry comprised 325 adult recipients of 649 islet infusions. (7) Three years after first infusion, 23% of islet-alone recipients were insulin-independent (defined as insulin-independent 2 or more weeks), 29% were insulin-dependent with detectable C-peptide, 26% had lost function, and 22% had missing data. Seventy percent achieved insulin independence at least once, 71% of whom were still insulin-independent 1 year later and 52% at 2 years. Factors that favored primary outcomes were higher number of islet infusions, greater number of total islet equivalents infused, lower pretransplant HbA1c levels, processing centers related to the transplant center, and larger islet size.

In 2008, Sutherland and colleagues reported on a study of outcomes for allogeneic islet recipients in the Collaborative Islet Transplant Registry compared to those of autologous islet recipients after complete pancreatectomy. (8) The authors concluded that the islet function is more resilient in autografts than in allografts. They noted that the 5-year insulin-independence persistence rate for autografts is similar to the 2-year rate for allografts. They mentioned that several factors unique to allograft cases are likely responsible for the differences, including longer cold ischemia time, diabetogenic immunosuppression, and auto- and alloimmunity.

In 2011, Thompson and colleagues in Canada published findings from a prospective cross-over study of intensive medical therapy (pretransplant) versus islet cell transplantation in patients with type 1 diabetes. (9) The article reported on 45 patients; at the time of data analysis, 32 had received islet cell transplants. Eight of 45 (18%) patients were no longer being followed; 5 dropped out pretransplant and 3 post-transplant. Two were lost to follow-up, 1 withdrew after graft failure, 2 withdrew due to persistent fatigue, 2 developed malignancy, and 1 had a severe CMV infection. Primary outcome measures are HbA1c, change in glomerular filtration rate (GFR), progression of retinopathy, and change in nerve conduction velocity. Median follow-up was 47 months pre-transplant and 66 months post-transplant. The overall mean HbA1c was 7.8% pretransplant and 6.7% post-transplant; this difference was statistically significant, p<0.001. In the 16 patients for whom sufficient data pre- and post-transplant were available on renal outcomes, the median decline in GFR (mL/min/month) was -6.7 pretransplant and -1.3 post-transplant (p=0.01). Retinopathy was assessed using the International Scale which categorizes nonproliferative diabetic retinopathy as mild, moderate, or severe. Retinopathy progressed in 10 of 82 (12%) eyes pretransplant versus 0 of 51 post-transplant (p<0.01). (The numbers of patients in the retinopathy analyses was not reported). The rate of change in nerve conduction velocity did not differ significantly between groups (exact numbers not reported). The authors noted that their finding of reduced microvascular complications after islet transplantation may be due, in part, to their choice of maintenance immunosuppression. The study used a combination of tacrolimus and mycophenolate mofetil (MMF). Additional studies with larger numbers of patients are needed to confirm the impact of islet transplantation on microvascular complications and the optimal immunosuppression regimen.

Recent papers have highlighted research in the areas of islet cell regenerative therapy including stem-cell technology, encapsulating islets to protect them from the host immune system by a semipermeable capsule, and xenotransplantation. (10-12) In addition, novel immunosuppressive regimens using biologics have also been discussed. (13)

Ongoing Clinical Trials
A comparison of strict glucose control with usual care at the time of islet cell transplantation (NCT01123122) (14): This is a single-center randomized controlled trial (RCT) comparing the impact of strict glucose control versus usual care prior to islet cell transplantation on outcomes in patients with type 1 diabetes. The primary study outcome is islet cell function 3 months post-transplantation. The estimated enrollment is 32 patients, and the estimated study completion date is September 2015.

Summary

Autologous islet transplantation is proposed in conjunction with pancreatectomy for patients with chronic pancreatitis. Although the published experience with autologous islet cell transplantation is limited, the procedure appears to significantly decrease the incidence of diabetes after total or near total pancreatectomy in patients with chronic pancreatitis. In addition, this procedure is not associated with serious complications itself and is performed as an adjunct to the pancreatectomy procedure. Thus, this may be considered medically necessary.

The techniques for allogeneic islet cell transplants are evolving, and the impact on net health outcomes is still uncertain. Moreover, longer follow-up with larger numbers of patients is needed before conclusions can be drawn about the safety of allogeneic islet transplantation and its impact on complications of diabetes mellitus. Thus, this is considered investigational.

Practice Guidelines and Position Statements

Guidance from the National Institute for Clinical Excellence (NICE), published in 2008, states that the evidence on allogeneic pancreatic islet cell transplantation for type 1 diabetes mellitus shows short-term efficacy with some evidence of long-term efficacy. (15) Evidence on safety shows that serious complications may occur, and the long-term immunosuppression required is also associated with risk of adverse events. The procedure is particularly indicated for patients with hypoglycemia unawareness or those already on immunosuppressive therapy because of renal transplantation. A 2008 update of guidance on autologous islet cell transplantation for improved glycemic control after pancreatectomy states that studies show some short-term efficacy, although most patients require insulin therapy in the long term. Complications mainly result from the major surgery involved in pancreatectomy rather than from the islet cell transplantation. (16)

Medicare National Coverage

Effective October 1, 2004, Medicare will cover pancreatic islet transplantation in patients with type 1 diabetes participating in the context of a clinical trial sponsored by the National Institutes of Health. (17) Partial pancreatic tissue transplantation or islet transplantation performed outside the context of a clinical trial will continue to not be covered.

References:


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