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Medical Policy Manual

Topic: Islet Transplantation

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Section: Transplant

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IMPORTANT REMINDER

Medical Policies are developed to provide guidance for members and providers regarding coverage in accordance with contract terms. Benefit determinations are based in all cases on the applicable contract language. To the extent there may be any conflict between the Medical Policy and contract language, the contract language takes precedence.

PLEASE NOTE: Contracts exclude from coverage, among other things, services or procedures that are considered investigational or cosmetic. Providers may bill members for services or procedures that are considered investigational or cosmetic. Providers are encouraged to inform members before rendering such services that the members are likely to be financially responsible for the cost of these services.

DESCRIPTION

Autologous islet transplantation is commonly conducted during pancreatectomy among patients with chronic pancreatitis. The procedure consists of isolating islet cells from the patient's resected pancreas using enzymes, and injecting a suspension of the cells back into the portal vein of the patient's liver, where the cells function as a free graft.

Allogeneic islet cell transplantation is normally conducted as a stand-alone procedure among patients with type 1 diabetes. Islet cells, harvested from a deceased donor's pancreas, are processed and injected into the recipient's portal vein.

Following each procedure, it is proposed that the beta cells in the transplanted islets will begin to make and release insulin.

Chronic Pancreatitis

Although the incidence of chronic pancreatitis is rising, it is still a relatively rare condition, affecting an estimated 7 to 8 new people out of every 100,000 people each year.[1] Some 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 cell transplantation, also called islet

autotransplantation (IAT), has been investigated as a technique to prevent this serious morbidity.

Type 1 Diabetes

Allogeneic islet cell transplantation potentially offers an alternative to whole-organ pancreas transplantation to treat type 1 diabetes, restore normoglycemia and ultimately reduce or eliminate the long-term complications of diabetes, such as retinopathy, neuropathy, nephropathy, and cardiovascular disease. However, a limitation of islet cell transplantation is that 2 or more donor organs are usually required for successful transplantation, and only pancreases rejected for whole-organ transplant are typically used for islet transplantation. Due to limited islet cell supply, allogeneic islet cell transplantation is recommended only for patients with frequent and severe metabolic complications who have consistently failed to achieve control with insulin-based management.

While most of the published research to date involves the transplantation of allogeneic human islet cells, there is also interest in xenotransplantation, using porcine islet cells.

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 cell transplantation must be conducted under FDA investigational new drug (IND) regulation. To date, islet cell transplantation has not received approval to be conducted outside the research setting.

MEDICAL POLICY CRITERIA

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

II. Autologous pancreas islet cell transplantation for all other indications is considered **investigational**.

III. Allogeneic and xeno islet cell transplantation, for any diagnosis, are considered **investigational**.

SCIENTIFIC EVIDENCE

Autologous Islet Cell Transplant as an Adjunct to Pancreatectomy

Autologous islet cell transplantation as an adjunct to pancreatectomy or near total pancreatectomy among patients with chronic pancreatitis has been investigated since 1977. Since then, the experience has grown slowly with incremental improvements in the islet cell isolation process. The current literature consists of several case series and systematic reviews.

Systematic Reviews

- In 2012, Bramis and colleagues searched for studies reporting on patients who had been treated with total, subtotal or completion pancreatectomy followed by islet autotransplantation.[2] Case series were included if they included more than five individuals and reported outcomes for consecutive patients. A total of 72 full-text articles were reviewed, and five studies were found to meet inclusion criteria. The postoperative insulin independence rate in the five 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 with a decrease in morphine use of 116 mg and 55 mg, respectively.

- A 2011 systematic review by Dong and colleagues included studies regardless of design or sample size.[3] After reviewing 84 studies, 15 observational studies were found to meet eligibility criteria. There were 11 studies of total pancreatectomy, two studies of partial pancreatectomy, and two 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 two 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 one year (reported by ten 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 one year (five studies) was 27% (95% CI: 21-33%) and at two years (three studies) was 21% (95% CI: 16-27%).

Randomized Controlled Trials

No randomized controlled trials for autologous islet cell transplantation as an adjunct to total or near total pancreatectomy were identified.

Nonrandomized Trials

Since the systematic reviews were published, one large single center series was reported. Sutherland and colleagues studied 409 patients with chronic pancreatitis who underwent total pancreatectomy and islet transplantation between February 1977 and September 2011.[4] 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.

Allogeneic Islet Cell Transplant

Islet cell transplantation has also been investigated as a treatment for type I diabetes, particularly in patients with poor glucose control despite insulin therapy.

The principal outcomes associated with treatment of type 1 diabetes are improvement in overall mortality rate, and reductions in rates of diabetic retinopathy, nephropathy, neuropathy, and cardiovascular disease normally associated with type 1 diabetes. In order to understand the impact of

islet cell transplantation for treatment of type 1 diabetes on these outcomes, well-designed randomized controlled trials (RCTs) that compare this therapy to standard medical treatment, such as insulin treatment, are needed. Further, an understanding of any adverse treatment effects, particularly those associated with life-long immunosuppressant therapy, must be carefully weighed against any benefits associated with islet transplantation to understand the net treatment effect of this therapy.

The current literature on allogeneic islet cell transplantation consists of a technology assessment, one RCT and several case series.

Technology Assessment

In April 2004, in its capacity as an Evidence-based Practice Center, the BlueCross BlueShield Association Technology Evaluation Center completed an evidence report on islet cell transplantation in type 1 diabetes for the Agency for Healthcare Research and Quality (AHRQ).[5] The report found that published data on clinical outcomes of islet-alone transplantation was limited by small patient numbers, few transplant centers, short duration of follow-up, and lack of standardized methods for reporting clinical outcomes. Efforts were ongoing to update and expand long-term transplant results, disseminate protocols to additional centers, and standardize reporting of outcomes.

The following statements from the report summarize available outcomes for patients highly selected for islet alone transplantation, based on a history of severe labile diabetes and/or hypoglycemia unawareness:

- The published technical success rate for islet-alone transplantation is high: 94% of transplanted patients achieved insulin independence over the 3-month post-transplant period. Clinical outcomes from presently available published data can be summarized as follows:
    - The published insulin independence rate at 1 year is 76% (37 patients; 3 centers). Recent abstracts report rates of 50% to 90% (104 patients; 4 centers).
    - The 2-year insulin independence rate is 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% to 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 were free of, or receiving, reduced insulin.
- Rare, serious adverse events have occurred in patients given allogeneic islet cell transplants; however, recent procedure modifications reportedly minimize risks of these adverse events. No procedure-related deaths, cytomegalovirus infection, or post-transplantation lymphoproliferative disease have been reported for islet alone transplantation.

The report concluded the evidence was insufficient for reaching conclusions regarding the following:

- Long-term complications of diabetes
- Quality of life outcomes

- Long-term consequences of immunosuppression
- Long-term effects of the islet graft
- The potential need for and consequences of supplemental islet transplants
- Islet-kidney transplants

Randomized Controlled Trials (RCTs)

Froud and colleagues randomized 16 type 1 diabetes mellitus patients to evaluate cultured islet transplantation with or without tumor necrosis factor (TNF-alpha) blockade using Infliximab just prior to islet infusion.[6] Insulin independence was achieved in 14 patients after 1 to 2 infusions, and was maintained in 11 patients after 1 year, and in 6 patients at 33 +/- 6-months without additional infusions. The authors reported no identifiable clinical benefit with the use of Infliximab, but concluded cultured human islet allografts produced results comparable to freshly transplanted islets including normalization of HBA1c. Further research in larger studies is needed to explore different immunosuppressive regimens.

Nonrandomized Trials

- In a landmark study, known as the Edmonton Protocol, 7 consecutive patients achieved insulin independence following islet cell transplants from 2 to 4 donors on a glucocorticoid-free immunosuppressive regimen.[7] However, 5-year outcomes from the first patients transplanted under the Edmonton protocol reported less than a 10% rate of insulin independence at 5 years, despite persistent graft survival as measured by C-peptide positivity (~80%).[8] The authors noted that problems with glycemic lability and hypoglycemia, the primary indications for transplant, were corrected; however, no clear advantages for chronic complications of diabetes (e.g., peripheral neuropathy) were evident. Chronic complications related to standard immunosuppressive therapy led to the need to alter the protocol in 23% of patients, thus leading the authors to conclude that "safer immunosuppression associated with fewer side effects is needed." Complications and side effects related to both immunosuppression and the procedure itself are also reported to be more common than originally thought.[9] The experience of the transplant center itself has a demonstrated effect on patient outcomes, with the more experienced centers reporting higher success rates.

- In 2012, Vantyghem and colleagues reported on 23 patients with type 1 diabetes who underwent islet transplantation; 14 had islet-only transplants and 9 had islet after kidney transplants. [10] Median HbA1c was 8.3% at baseline and 6.7% at 3 years. Ten of the 23 patients (43%) were insulin independent 3 years after islet transplantation. Findings were not reported separately for the islet-only transplant recipients.

- In 2006, Shapiro reported on 36 patients with type 1 diabetes mellitus that had undergone islet transplantation.[11] While short-term results were promising, insulin independence was generally not sustainable; only 5 patients were insulin-independent at two years.

- In 2011 Thompson et al. reported on a prospective cross-over study of intensive medical therapy (pre-transplant) versus islet cell transplantation among 32 patients with type 1 diabetes.[12] Following enrollment in the study, median follow-up was 47 months pre-transplant and 66 months post-

transplant. Although improvements in HbA1c, retinopathy progression, and renal function were seen in the transplant group, small sample size and lack of treatment randomization limit interpretation of these findings. The authors also 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).

- Several other small case series have focused on identifying alternatives to current transplant techniques, studying encapsulated islet transplantation without immunosuppression,[13] optimizing single versus multiple-donor transplantations,[14] and comparing whole pancreas transplant to islet cell transplantation.[15,16] Recent research also addresses islet-after-kidney transplantation.[17] However, results from these studies should be interpreted with caution as the small sample sizes ($n \leq 66$), lack of randomized treatment allocation and/or appropriate comparison groups do not allow for ruling out chance as an explanation of findings.

Current non-randomized studies of allogeneic islet cell transplantation appear to suggest an initial benefit (such as a decline in HbA1c levels, for example) associated with the transplant. However, as a recent review of this therapy notes:[18]

> "[O]ne cannot be certain of the claim that partially failed islet transplantation leads to the use of less insulin and less hypoglycemia on a cause-effect basis. It could just as easily be that patients who enter transplant programs come under close clinical scrutiny by interested diabetologists who begin managing them more skillfully."

Additional randomized controlled trials are needed to determine the strength and magnitude of potential benefits associated with this therapy and to isolate such the impact of such benefits from standard medical care.

Registry Data

- Bretzel and colleagues reported on data collected from the International Islet Transplant Registry from 1999-2004.[19] Data were available for 458 human islet cell transplantations. At 1-year post transplant, patient survival was 97%, islet grafts were functioning in 82% of the cases, and insulin independence was achieved in 43% of the cases.

- Founded in 2001 by the National Institute of Diabetes, Digestive and Kidney Diseases, the Collaborative Islet Transplant Registry (CITR) has been collecting information on allogeneic islet transplantation in North America, Europe, and Australia. The most recent peer-reviewed publication of CITR data was published in 2012.[20] . The update focused on changes in outcomes over time in 677 patients, all of whom received a transplant as of December 31, 2010 (n=575 islet-only; n=102 kidney+islet). Unfortunately, outcomes presented in this report were limited by considerable levels of missing data which increased with longer follow-up. The missing data were reported to be a mixture of unavailable medical records and data still pending entry into the registry.

  The authors reported improved insulin independence at three years post-transplant, from 27% in the early era (1999–2002, n = 214) to 37% in the mid era (2003–2006, n = 255) and 44% in the most recent era (2007–2010, n = 208; P = 0.006 for years-by-era; P = 0.01 for era alone). However, not all recipients in the latter era had reached the 3-year milestone at the time of this updated report. The need for islet reinfusion for loss of function of first graft by 1-year decreased significantly from 60-65% in 1999-2006 to 48% in 2007-2010 ($p<0.01$). There was also a modest decrease in clinically

reportable adverse events in the 2007-2010 era, from 50-53% in 1999-2006 to 38% in 2007-2010. The rates of peritoneal hemorrhage or gallbladder infusion were 5.4% in 1999-2003 and 3.1% in 2007-2010. The authors did not report findings separately from the subset of patients who underwent islet-only transplants.

- The Institute for Clinical and Experimental Medicine (IKEM), based in the Czech Republic, published results from a retrospective analysis of a registry of all patients receiving one or more allogeneic or autologous islet transplants from 2005 to 2010 (n=15 and n=5, respectively).[21] Although islet function was documented in 11 of 15 and 3 of 5 patients, respectively, after 12 months (as indicated by C-peptide levels), only 1 patient receiving an allogeneic transplant was able to achieve independence from insulin beyond 12 months. The authors conclude that islet transplant may be best suited for high-risk recipients, as "routine clinical application is still hampered by the limited availability of usable organ transplants and viability of transplanted islets."

Results from the above registry reports should be interpreted with caution as these registries are not reflective of the complete North American experience with islet transplants; not all transplant centers participated in each regional endeavor, nor is data complete for all those who do participate. Therefore, there may be inherent bias in the data. The focus on intermediate outcomes, instead of long-term health outcomes, also limits interpretation of these findings.

Xenotransplantation

Although there is research interest in porcine islets as an alternative and potentially unlimited source of islet cells, current data from human clinical trials is limited to two case series.

- In 2011, Wang and colleagues published results from a small clinical trial on the safety and feasibility of neonatal pig islets (NPIs) in 22 patients in China.[22] However, only 6 of the 22 patients were subsequently followed for more than 2 months, limiting conclusions about the long-term use of NPIs.
- Also in 2011, Esquivel-Pérez and colleagues published a report on 23 patients not on immunosuppression, transplanted with a porcine cell-filled device.[23] Following an average of 5.7 years post-transplantation, the researchers reported that the patients with the lowest levels of antibodies were significantly more likely to report higher insulin dose reductions. However, not all patients were able to attain low levels of antibodies, for reasons not clearly known. Therefore, this report provides evidence for transplantation protocols but does not address the clinical utility of xenotransplantation.

Current literature has not directly addressed problems related to xenograft rejection and xeno-zoonosis (transmission of animal disease to humans).

Clinical Practice Guidelines

In 2006, the American Diabetes Association (ADA) published a position statement, based on a systematic review of the evidence, on the use of pancreas and islet transplantation in type 1 diabetes.[24] While highlighting the potential advantages of islet transplantation over current treatment options for type 1 diabetes, the ADA ultimately recommended against the use of this procedure outside the research setting, stating, "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."

Summary

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

- Although research is ongoing, the data published to date are inconclusive with respect to the role of, and final health outcomes associated with, islet cell transplantation in the treatment of type 1 diabetes. Attempts to achieve insulin independence and stabilization of secondary complications of diabetes have been complicated by difficulty in isolating sufficient numbers of islets and by immunosuppression regimens with diabetogenic side effects. Additionally, the U.S. Food and Drug Administration (FDA) has not yet granted full market approval for islet cell transplantation. Therefore, islet transplantation is considered investigational in the management of type 1 diabetes.

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CROSS REFERENCES

Pancreas Transplant, Transplant, Policy No. 6

CODES	NUMBER	DESCRIPTION
CPT	48160	Pancreatectomy, total or subtotal, with autologous transplantation of pancreas or pancreatic islets
	48999	Unlisted procedure, pancreas
HCPCS	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
	S2102	Islet cell tissue transplant from pancreas; allogeneic