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Evidence Report/Technology Assessment

Number 98

Islet Transplantation in Patients with Type 1 Diabetes Mellitus

Summary

Introduction

Pancreatic islets are small clusters of endocrine cells in the pancreas that include insulin-producing beta cells. In type 1 diabetes—also known as juvenile or insulin-dependent diabetes—the body's immune system specifically destroys the beta cells, resulting in a loss of insulin production. Pancreas transplants have been used as a way to restore insulin production, but require long-term treatment to prevent immune rejection of the transplanted organ. Islet transplantation offers a potential alternative to whole-organ pancreas transplantation, but early attempts rarely succeeded. Following the introduction of the Edmonton transplant protocol in 1999, developed at the University of Alberta in Canada, major islet transplant centers have developed and refined new procedures, are enlisting patients into clinical studies and following their progress, and are reporting detailed data to a new transplant registry. This report represents the current state of the evidence in a field where clinical research is actively progressing.

Whole-organ pancreas transplants were initially performed in patients with type 1 diabetes who were undergoing kidney transplants (for kidney failure), with the pancreas transplanted either at the same time as the kidney or in a later operation. Compared with patients receiving only a cadaver kidney transplant, patients receiving a simultaneous pancreas–kidney transplant have improved long term survival—although immediately after surgery, during the early post-transplant period, survival is worse.[1–3] Transplant of a pancreas together with a kidney also has positive effects on low blood sugar/hypoglycemia,[4,5] kidney complications,[6,7] and high blood pressure/hypertension.[8]

Over the past decade, pancreas transplant alone (PTA) has been used selectively in some type 1 diabetes patients. Patients considered for this approach are those for whom the potential benefit of the procedure is expected to offset the adverse consequences of lifelong immunosuppressive therapy, which keeps their immune system from rejecting the transplanted organ. PTA is recommended only for patients with a history of frequent and severe metabolic complications, severe and incapacitating clinical and emotional problems with receiving insulin shots, or consistent failure of insulin-based management to prevent acute complications.[9] The results of the Diabetes Control and Complications Trial (DCCT) demonstrate that intensive insulin therapy significantly improves control of blood sugar (glucose) levels and reduces the risk of secondary complications, such as eye problems, nerve damage, kidney damage, and cardiovascular disease.[10] However, there is a small population of patients with unstable type 1 diabetes who, nevertheless, have difficulty maintaining glucose control with administration of insulin injections. Some of these patients develop severe hypoglycemia without the usual associated warning signs.[11] Untreated, severe hypoglycemic episodes may result in coma, seizures, and death. Such patients may require constant supervision by a family member or caretaker. Following the introduction of the Edmonton protocol, islet transplantation has largely been used in patients who are candidates for PTA; most have been selected due to their severe and frequent hypoglycemic episodes.

Transplanted islets are infused into the portal vein through a catheter and lodge in the liver. Because islet transplantation does not require a large abdominal incision, it is a less-invasive alternative to whole-organ transplantation and avoids the unhealthy side-effects of complex surgery. However, early protocols resulted in only around 10 percent of patients achieving insulin independence at 1 year after the procedure. Nevertheless, interest in this approach remained

high due to improvement in long-term diabetic consequences in studies of islet-transplanted animals and in those patients undergoing islet transplant who were able to maintain insulin independence. For example, in the pre-Edmonton era, one center reported reduced cardiovascular mortality and kidney damage in their few patients with long-term, successfully transplanted islets.[12]

Improved results for insulin independence and maintenance of normal blood glucose levels have been achieved with newer protocols that use a low-dose immunosuppressive therapy without glucocorticoid drugs, improved islet preparation, and infuse a minimum islet mass of 9,000 islet-equivalents per kilogram (IEq/kg) of body weight. The first of these protocols was the Edmonton protocol;[13] subsequent protocols have been developed at other centers (e.g., Universities of Minnesota and Miami).[14,15] As interest in establishing new islet transplant centers increases, institutional collaborations with established preparation centers will play a large role due to the startup costs for an islet preparation facility, regulatory issues, and complexity of the isolation procedure.[16] Currently, the Division of Clinical Research at the National Institutes of Health's National Center for Research Resources, supports 10 Islet Cell Resource Centers in the U.S. These centers isolate, purify, characterize, and distribute human pancreatic islets for subsequent transplantation in approved clinical protocols (for additional information see http://www.ncrr.nih.gov/clinical/cr_icr.asp)

Currently, a limitation on transplanting islets is that two or more donor organs are usually required for successful transplantation. The low availability of donor pancreas organs limits the number of pancreas or islet transplants that can be performed. For 2002, the Organ Procurement and Transplantation Network reported 6,187 total deceased organ donors, 1,870 pancreas organs recovered, and 1,461 pancreas organs transplanted.[17] A smaller, unreported number of pancreas organs are also collected and preserved (harvested) specifically for islet transplantation research.[18] In contrast, a total of 9,691 individual kidneys were harvested and transplanted from the same group of organ donors.

Islet preparations are subject to regulation by the U.S. Food and Drug Administration (FDA) as biological products and as drugs. Because the use of cells derived from whole organs meets the criteria for a biologic product to be regulated under the Public Health Service Act, the FDA classifies transplantation of allogeneic (not genetically identical to the recipient) islets as somatic cell therapy, which requires premarket approval.[19] Islets also meet the definition of a drug under the Federal Food, Drug, and Cosmetic Act. Clinical studies to determine the safety and effectiveness outcomes of allogeneic islet transplantation must be conducted under FDA's investigational new drug (IND) regulations. At least 35 IND applications have been submitted to the FDA,[19] but, as of this writing, no center has as yet submitted a biologics license application.

Outcomes of interest to the authors of this evidence report are early and long-term clinical diabetic outcomes, biologic outcomes that are indicators of graft function and glycemic (blood-sugar) control, and adverse outcomes. Early clinical outcome measures are insulin independence, percent of prior insulin use, hypoglycemic episodes, and quality of life. For patients with type I diabetes, improvement in long-term diabetic outcomes is the measure of ultimate success of islet transplantation. The objective is to reduce or eliminate long-term diabetic complications such as eye disease, nerve damage, kidney damage, and cardiovascular disease. Measurement of C-peptide and HbA1c (glycated hemoglobin) are biological outcomes that are indicators of graft function and glycemic control, respectively. Potential adverse events of islet transplant may be direct consequences of the procedure (for example, hemorrhage or thrombosis from through-the-skin access to the portal vein) or the continued immunosuppression needed to maintain viability and function of the transplanted islets. Adverse effects of immunosuppression may be near-term (such as mouth ulceration, diarrhea, or anemia) or long-term (including kidney disease, post-transplant cancers of the immune system, other cancers, and cytomegalovirus or other infections).

A consensus definition of successful islet transplantation was proposed at a recent meeting of the FDA Biological Response Modifiers Advisory Committee: restoration of sustained euglycemia with no or a reduced exogenous insulin requirement.[20] Clinical outcome parameters that can be used to measure success are insulin independence or percent of prior insulin use, frequency and severity of hypoglycemic episodes, and quality of life. However, in the absence of well-controlled and well-reported studies, insulin independence is the most persuasive measure available to establish the success of the procedure.

The National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) initiated and funded the Collaborative Islet Transplant Registry (CITR) in September 2001. The CITR will develop and implement reporting standards, compile data on islet transplants in the U.S. and Canada, and perform and communicate analyses of outcomes (http://spitfire.emmes.com/study/isl/index.html). Unfortunately, the first CITR report was not yet available at the time this evidence report was prepared. In the future, the Registry will be the most comprehensive source of data on the outcomes of islet transplant. While the CITR will provide aggregated data on outcomes, published studies from individual centers still remains the best source of detailed results and of data on center-specific outcomes.

Methods

As much as possible, the protocol for this review was designed prospectively to define: study objectives; search strategy; patient populations of interest; study selection criteria; outcomes of interest; data elements to be abstracted and

methods for abstraction; and methods for study quality assessment.

The report addresses the following four key questions:

1. *What are the outcomes for selected diabetes patients treated with islet transplantation compared with similar patients who receive whole-organ pancreas transplants or medical (nontransplant) management of their disease? Are similar outcomes achievable outside of the investigational setting?*
2. *What criteria should be used to select patients for islet transplantation and what are the outcomes for relevant patient subgroups?*
3. *What are the incidence and severity of adverse effects associated with the islet transplantation procedure and with the immunosuppressive regimens? How do these compare with the adverse effects associated with whole-organ pancreas transplantation or medical management?*
4. *What is the evidence that the insulin independence or significantly reduced insulin dependence achieved with islet transplantation can be maintained long-term after the initial transplant, or with additional transplants in the event of failure of the original procedure? How often must successive transplants be performed?*

This report is limited to transplantation of unaltered human allogeneic islets harvested from donor organs. Thus, cultured islets from donor organs are included, but the following are excluded: autologous islets (from the patient's own pancreas), islets from pig pancreas, genetically altered islets, and islets prepared from stem cells.

The MEDLINE database was searched through October 2003 for recently published research articles and for relevant background information. Search was limited to articles with an English-language abstract. Bibliographies of relevant articles were also searched and the project's Technical Expert Panel was queried for additional relevant articles. Registry data, recent meeting abstracts, and presentations by investigators from key research centers were also sought.

For all of the key questions, studies were included if they:

- reported prospective trials of islet transplantation; AND
- reported on outcomes of interest with at least 3 months of followup; AND
- used a transplant protocol based on the Edmonton protocol or a subsequently developed protocol designed to improve upon aspects of the procedure; AND
- provided sufficient details on trial design, methods, and outcomes to assess study quality; AND
- were available as a full-length publication, abstract, or poster/slide presentation provided by the original presenter.

All abstracts initially retrieved by the search strategy were reviewed by one researcher who also reviewed the full-text articles to determine whether study selection criteria were met. Selected papers were abstracted by a single reviewer and evidence tables were fact-checked by a second reviewer. After initial review of the evidence on islet transplantation, the decision was made that it was premature to compare this technique with whole-organ pancreas transplants; hence, a systematic review of the evidence on pancreas transplant outcomes was not undertaken for this report.

Results

Although more than 2,000 abstracts were reviewed, almost all indexed clinical studies were completed prior to the adoption of the Edmonton protocol. As a result, few articles were retrieved and included in this review. Of the studies relevant to the Edmonton protocol, only 12 published articles[13,14,16,21–29] reported efficacy and adverse outcomes, and two additional articles[30,31] reported only adverse outcomes.

Due to the scarcity of published articles, abstracts and presentations from five scientific conferences were reviewed, and those meeting the selection criteria were summarized as supplementary sources that provide preliminary results of studies anticipated to be fully reported in the next 2 years. Because summary data from the CITR is not yet available, a summary of results from transplant groups attending the 2002 Second Annual Annenberg Symposium, in Rancho Mirage, CA, represents the only available effort to collate islet transplant data from active centers and is also included in this report.

It was not possible to summarize and pool together the most recent outcomes from each reporting center for several reasons. First, some centers reported different outcomes on different numbers of patients in more than one publication, precluding an accurate synthesis. Second, different centers reported the same type of outcome in different ways. Thus, a standardized data collection, such as that in progress by the CITR, will be needed for an accurate and complete data summary. For these reasons, data in this report are generally presented by center. Moreover, reports on the outcomes of islet transplantation from a single center often combine results from patients treated on different protocols. Protocol characteristics are noted in the evidence tables for published reports, but this review makes no attempt to compare the outcomes of different protocols.

Published data on the clinical outcomes of islet-only transplantation are limited by small patient numbers, few transplant centers, short duration of followup, and by lack of standardized methods of reporting outcomes. Data are also lacking on quality-of-life outcomes. Meeting abstracts and presentations supplemented published reports with larger numbers of patients and reporting transplant centers. Efforts are ongoing to update and expand long-term transplant results and quality-of-life data, disseminate protocols to additional centers, and standardize reporting of outcomes. The available evidence is summarized below:

- Islet-alone transplantation has been used in a highly selected population of type 1 diabetic patients who have been selected for transplantation based on a history of frequent and severe metabolic complications, severe and

incapacitating clinical and emotional problems with exogenous insulin therapy, or consistent failure of insulin-based management to prevent acute complications.

- There are sufficient data to conclude that there is a high rate of technical success for islet-alone transplantation. Five centers published reports[14,16,21,25,29] on 47 patients who completed a transplant protocol. Of these, patients 44 (94 percent) achieved insulin independence over the 3-month post-transplant period.
- Clinical outcomes from presently available data can be summarized as follows:
  - Published data from three centers[14,21,29] report that 28 of 37 patients (76 percent of those completing a transplant protocol) maintained insulin independence for 1 year. Four centers that followed 104 patients for at least 12 months report insulin independence in 50 to 90 percent of patients in recent abstracts.
  - Only one published study (from the Edmonton group)[22] reported four of six patients remained insulin independent after 2 years of followup. In one abstract from Edmonton, 48 patients underwent transplantation and 15 were followed for 2 or more years. Statistical analysis estimated that the probability of remaining insulin-independent at 2 years was 64 percent.
  - Two institutions published[14,22] detailed information on 23 transplant patients who had at least 1 year of followup. Of these, 19 (83 percent) had normal blood-sugar levels without hypoglycemic episodes (were euglycemic), and needed no or reduced amounts of additional insulin.
  - All published series report that hypoglycemic episodes were less frequent or intense in insulin-independent transplant patients. In three series[14,22,29] reporting on 26 patients who completed the transplant protocol, hypoglycemic episodes were also reduced in nine patients who exhibited continued C-peptide secretion, but who were not insulin independent at 1 year. Abstracts report this outcome less consistently but, where reported, hypoglycemic episodes were eliminated in insulin-independent patients.
  - In each published series[14,16,22,25,26,29] and for all insulin-independent patients, mean HbA1c decreased from greater than 7 percent to less than 6.5 percent; 7 percent or less is recommended to avoid or delay progression of diabetic complications. Where reported in meeting abstracts, in most cases the mean HbA1c level after transplantation was less than 6.5 percent; this level, was maintained for up to 3 years post-transplant in two series (13 patients reported on, total).
- Data are scant on the effects of islet transplantation on long-term diabetic consequences. In one publication,[22] the Edmonton group reported on 17 subjects who completed the transplant protocol. Damage to the retina progressed in three patients and required laser photocoagulation treatment. Nine patients either started or increased treatment for high blood pressure. Cholesterol rose in 15 patients, of whom 11 required statin therapy. There were no major changes in nerve damage. Serum creatinine and urine protein levels only showed significant changes in two patients with pre-existing kidney disease.
- Infrequent but serious adverse events (such as portal vein thrombosis or hemorrhage) have occurred in patients given islet transplants, but it is not possible from present data to estimate their frequency.[14,21,29] Recent changes in the transplant procedure reportedly minimize the risks of these adverse events. No procedure-related deaths have been reported among patients who received islets alone. Notably, no publication or abstracts reported cytomegalovirus infection in any patients given islet-only transplants. Post-transplant immune system cancers also have not been reported so far, but this may reflect the small number of subjects studied.
- The available evidence is insufficient to evaluate the long-term consequences of immune system suppression, any long-term effects of the islet graft, and the potential need for and consequences of supplemental islet transplants.
- The majority of transplants using the newer protocols have been of islets alone. However, it has been reported (mainly in meeting abstracts and presentations) that 30 islet transplants after or simultaneous with kidney transplants have been attempted; in most cases, followup is less than 1 year. The present evidence is insufficient to permit conclusions for this type of transplant.

Discussion

The available evidence demonstrates the technical feasibility and superior procedural success of islet transplantation using the Edmonton and more recent protocols. Where 1-year followup has been reported, most patients are insulin independent and free of severe hypoglycemic episodes. At present, 100 or more patients have been followed for 1 year after transplantation, and the Edmonton group recently reported on 15 patients followed for 2 years or more. Evidence on longer-term outcomes or durability of the procedure is not yet available. Therefore, it is not yet possible to assess the effects on diabetic complications or the consequences of lifelong immunosuppression.

Reports from the CITR are expected in the near future. These will provide systematic data on outcomes of patients treated at the major islet transplant centers, and will eventually accumulate data on long-term outcomes. The CITR plans to collect data on patient characteristics at transplantation (for post-Edmonton protocols only, and including retrospective data) as well as long-term followup data on the secondary complications of diabetes. The addition of data on the presence and severity of retinopathy, nerve damage, and other diabetic complications in the patients prior to transplantation

would aid the interpretation of long-term results. Randomized, controlled trials of islet transplantation (in direct comparison to no treatment or whole-organ transplantation) do not exist and are unlikely to be conducted. Thus, pre- and post-procedure evaluations, which are likely to be the only source of evidence to evaluate this procedure, should proceed with the utmost rigor.

As is the case with many medical or surgical procedures, outcomes may vary by center due to the transplant team's experience or specifics of the treatment. Moreover, such variation can be difficult to discover when the number of procedures is too small to reach firm statistical conclusions. Center-specific data will complement aggregate data in evaluating the outcomes of islet transplants, setting standards for performance, and improving outcomes.

Long-term followup will outline the durability of islet graft function and the need for repeat procedures. Uncertainties remain: Should patients who fail to maintain insulin independence be administered additional islet transplants? Does reactivation of autoimmune reactions against beta cells affect the success of subsequent transplants? Do the risks of the procedure increase with successive transplants?

At present, the supply of donor pancreases stringently limits the availability of islet transplants. However, refining the islet isolation and transplant procedures could promote more vigorous efforts at organ collection, and perhaps make islet transplantation more available. Simultaneous transplant of islets and kidneys is being attempted and may represent another population of patients using islet transplantation. Ongoing research on innovations in immunosuppression regimens, and in techniques to prevent rejection or induce tolerance of transplants, may eventually improve the benefit-to-risk ratio of the procedure; methods of *in vitro* production may also increase the availability of islets for transplantation. While pancreas and islet transplantation are now the only means of achieving physiologic insulin regulation, continuous glucose monitoring and **insulin** infusion technologies are being developed in hope of someday developing an artificial pancreas. As innovations in the management of type I diabetes emerge, risks and benefits, relative-effectiveness, and cost-effectiveness for various patient populations should be carefully evaluated.

Availability of the Full Report

The full evidence report used to create this summary was taken was prepared for the Agency for Healthcare Research and Quality, by the Blue Cross and Blue Shield Association Technology Evaluation Center Evidence-based Practice Center, under Contract No. 290-02-0026. It is expected to be available late in the summer of 2004. At that time, printed copies may be obtained free of charge from the AHRQ Publications Clearinghouse by calling (800)-358-9295. Inquiries should include a request for Evidence Report/Technology Assessment No. 98, Islet *Transplantation in Patients with Type 1 Diabetes Mellitus*. In addition, Internet users will be able to access the report and this summary online through AHRQ's Website at www.ahrq.gov

Suggested Citation

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