Chapter 2. Methods

This report is the product of a systematic review of the evidence on the outcomes of islet transplantation for type 1 diabetes mellitus.

The protocol for this review was designed prospectively as much as possible 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.

This chapter of the report describes the objectives, key questions, and search strategies used to find articles; the criteria and methods for selecting eligible articles; the methods for data abstraction; the methods for quality assessment; and finally, the peer review and technical assistance received during the project.

Objective and Key Questions

The overall objective of this report is to systematically review and synthesize available evidence on the outcomes of islet transplantation in patients with type 1 diabetes who lack functioning islets. The report's scope is limited to transplantation of unaltered human allogeneic islets harvested from donor organs. Thus, cultured islets are included, but the following are excluded: autologous islets, porcine islets, genetically altered islets, and islets prepared from stem cells.

Relevant evidence for this review only includes studies that used the Edmonton protocol or subsequently developed protocols. Outcomes of islet transplants using earlier procedures than the Edmonton protocol were summarized briefly in the Introduction chapter of this review. They are considered relevant evidence only insofar as they may contribute to a causal chain that can be linked to outcomes of islet transplants using the Edmonton or subsequently developed transplant protocols.

To achieve these objectives, the report addresses the following key questions:

1. What are the outcomes of managing selected diabetes patients with islet transplantation compared with similar patients receiving whole-organ pancreas transplant or medical management? 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? Relevant subgroups include:
    - patients with severe or uncontrolled diabetes symptoms such as hypoglycemia unawareness despite (or due to) intensive medical management;
    - patients with prior, failed, whole-organ pancreas transplant (i.e., have already met eligibility criteria for pancreas transplant alone [PTA]);
    - patients with existing, functioning kidney transplants or who are candidates for kidney transplant and will thus be on immunosuppressive therapy;
    - special patient populations, including women, racial and ethnic minorities, pediatric and elderly populations, and those of low socioeconomic status.

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 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? How often must successive transplants be performed?

An initial review of the islet transplant literature revealed the following limitations: small patient sample sizes from a small number of islet transplant centers; relatively short followup times; and, variably reported outcomes. These limitations precluded a comparison of islet transplant outcomes with those for whole organ pancreas transplantation. Thus, a formal literature search and data abstraction on the clinical outcomes of whole-organ transplantation was not attempted and whole-organ transplantation was instead summarized in the Introduction chapter.

Search Strategy

Available registry data, recent meeting abstracts and presentations by investigators from key research centers are the primary sources of evidence for Key Questions 1–4. The MEDLINE database was searched for recently published research articles and for relevant background information. The database was searched initially from 1966 through October, 2002; subsequent search updates were performed through October, 2003. Additionally, bibliographies of relevant articles were also searched and the project's Technical Expert Panel was queried for any relevant articles omitted from the search results. During the peer review process, reviewers informed the Evidence-based Practice Center (EPC) staff of articles recently published or accepted for publication and in the case of certain imminent publications, provided prepublication manuscripts.

The search strategy selected for review all citations that included any of the following terms:

"Islets of Langerhans Transplantation"[Medical Subject Heading® (MeSH®)];
"Islets of Langerhans"[MeSH®] AND "transplantation"[MeSH®];
islet*[tw] AND transplant*[tw]; or
beta cell*[tw] AND transplant*[tw].

The search was limited to studies on human subjects with English-language abstracts. Papers published in foreign languages were reviewed if the English abstract appeared to meet inclusion criteria. No studies relevant to the evidence review were published in a language other than English.

Study Selection Criteria

For all key questions in this report, studies were included if they:

1. reported prospective series of islet transplantation; AND
2. reported on outcomes of interest with at least 3 months of followup (1 year preferred); AND
3. used a transplant protocol based on the Edmonton protocol or a subsequently developed protocol; AND
4. provided sufficient details on study design, methods, and outcomes to assess study quality (see below); AND
5. were available as a full-length publication, abstract, or poster/slide presentation provided by the original presenter.

Patients

Patients of interest for this review were those with long-standing type 1 diabetes mellitus based on a stimulated serum C-peptide concentration of less than 0.48 ng per milliliter; whose glucose concentration remained uncontrolled despite exogenous insulin therapy; who had episodes of severe hypoglycemia requiring assistance or labile diabetes with evidence of daily lifestyle disruption; and had no comorbidities precluding transplantation or immunosuppression therapy. In general, eligible patients were judged by the treating centers to be at greater risk from uncontrolled diabetes than they would be from the global risk of transplantation and immunosuppression.

Outcomes of Interest

The outcomes of interest are grouped into near-term and long-term efficacy outcomes and adverse events. Near-term efficacy outcomes include clinical outcomes:

- proportion of patients remaining insulin independent at yearly intervals after transplantation;
- percentage of baseline insulin use at yearly intervals after transplantation; and
- severe episodes of hypoglycemia.

Biological outcomes include:

- C-peptide levels;
- hemoglobin A1c.

Long-term efficacy outcomes include effects on complications of diabetes, such as:

- nephropathy;
- retinopathy;
- atherosclerosis, etc.

Adverse outcomes include those related to the islet infusion procedure, such as:

- mortality;
- bleeding;
- thrombosis;
- pain;

and those related to the immunosuppressive regimen:

- mortality;
- nephrotoxicity;
- hypertension;
- hypercholesterolemia;
- thrombocytopenia;
- leukopenia;
- infection;
- post-transplant lymphoproliferative disease.

Additional adverse outcomes of interest are:

- possible long-term effects of islets; and
- need for additional transplants.

Methods of the Review

Article Selection

All abstracts initially retrieved by the search strategy were reviewed by one researcher who also reviewed the fulltext articles to determine whether study selection criteria were met (MP). Selected papers were abstracted by a single reviewer (MP or JS) and evidence tables were fact-checked by a second reviewer (MP or JS).

Although a total of 2,052 abstracts were initially reviewed, very few articles were retrieved as almost all indexed clinical studies were completed prior to the adoption of the Edmonton protocol. Of the studies relevant to the Edmonton protocol, the vast majority were reviews, animal studies, or technical reports. Including articles published and retrieved during the preparation of this review, only 12 published studies (Owen, Ryan, O'Kelly, et al., 2003; Ryan, Lakey, Paty, et al., 2002; Paty, Ryan, Shapiro, et al., 2002; Johnson, Kotovych, Ryan, et al., [In press]; Markmann, Deng, Huang, et al., 2003; Goss, Schock, Brunicardi, et al., 2002; Kaufman, Baker, Chen, et al., 2002; Shapiro, Lakey, Ryan, et al., 2000; Ryan, Lakey, Rajotte, et al., 2001; Markmann, Deng, Desai, et al., 2003; Hering, Kandaswamy, Harmon, et al., 2004 [In press]; Hirshberg, Rother, Digon, et al., 2003) reported efficacy and adverse outcomes, and 2 additional (Casey, Lakey, Ryan, et al., 2002; Goss, Soltes, Goodpastor, et al., 2003) reported only adverse outcomes.

Additional sources of evidence. Due to the scarcity of published articles, additional sources of evidence were sought. Abstracts and presentations from scientific conferences were reviewed, and those meeting study selection criteria are summarized in this review as supplementary

sources that provide preliminary results of studies anticipated to be fully reported in the next 2 years. The scientific conferences reviewed were:

- XIX International Congress of the Transplantation Society; 2002 August 25-30; Miami, FL (abstracts searched)
- City of Hope Rachmiel Levine Symposium; 2002 October 9-12; Anaheim, CA (attended)
- Islet Transplantation 2002 and Beyond: 2nd Annual Annenberg Symposium; 2002 December 5-7; Rancho Mirage, CA (attended)
- American Transplant Congress 2003: The Fourth Joint American Transplant Meeting, May 30, 2003 - June 4, 2003, Washington, DC (abstracts searched)
- 9th Congress of the International Pancreas and Islet Transplant Association. 8-11 July 2003, Dublin, Ireland (abstracts searched)
- 1st Islet Transplant Congress; 2003 November 13-16; Miami Beach, FL (attended)

In the future, the most comprehensive source of data will be the Collaborative Islet Transplant Registry (CITR), which is initiated and funded by the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK). The registry is coordinated by the EMMES Corporation of Rockville, Maryland; Dr. Bernhard Hering of the University of Minnesota is the Medical Director.

CITR was initiated in September 2001. CITR is collecting extensive, retrospective data on all patients who have received islet transplants using Edmonton or subsequently developed transplant protocols, and will maintain an ongoing data collection process for new patients. The data elements are more comprehensive than those collected by the previous International Islet Transplant Registry, and require original data entry (i.e., data from the International Islet Transplant Registry has not been downloaded into the CITR database).

As of November 2003, CITR was still collecting data from the participating institutions. Thus, data and analyses from CITR were not available for this evidence report.

Technical Expert Panel and Peer Review

The development of this evidence report was subject to extensive expert review including ongoing guidance from a Technical Expert Panel (TEP) and document review by the TEP and by a panel of designated peer reviewers (Appendix B lists the members of the Technical Expert Panel and external peer reviewers).

TEP members provided ongoing guidance and review on all phases of this project including review of the draft report.

The draft report was also reviewed by a panel of external peer reviewers that included experts in endocrinology, pancreas transplantation, and islet transplantation, as well as a patient advocacy representative. Reviews were also solicited from the Immune Tolerance Network (ITN; currently overseeing multicenter studies of the Edmonton protocol), the Juvenile Diabetes

Research Foundation (currently funding, along with the National Institutes of Health, ITN studies of the Edmonton protocol), and the American Diabetes Association. Comments were elicited from external peer reviewers using a structured comment form, compiled, and submitted with a description of comment disposition to the Agency for Healthcare Research and Quality.