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Original Research

Clinical Islet Transplantation for Type 1 Diabetes in Canada: Referral Patterns and Eligibility Assessment

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Key Messages

- The majority of applications for consideration for islet transplantation come directly from people with diabetes.
- Approximately 80% of applications were ineligible for islet transplantation.
- 39% of subjects had no indication for transplant (severe hypoglycemia or glycemic lability) and the most common contraindications were non-optimised insulin regimen, renal dysfunction or desire for future pregnancy.

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ABSTRACT

Objectives: Careful selection for clinical islet transplantation (CIT) is required because of limited organ supply and the risks for lifelong immunosuppression. However, the indications for this novel treatment may not be widely known, and selection criteria continue to evolve. We sought to describe the pattern of referrals to our centre and the most common factors determining eligibility for CIT.
Methods: We performed a retrospective chart review of all applications for CIT received at the University of Alberta between May 2009 and April 2012. Demographics and clinical data were abstracted along with the sources of referral. Application results and reasons for eligibility or ineligibility were determined. For ineligible subjects, the primary reason for ineligibility was noted.
Results: We received 246 applications (mean age 43; range, 13 to 78 years; 54% male) from across Canada. The majority (81%) were self-referrals, with the remainder coming from specialists (15%) or primary care physicians (4%). Of the applicants, 19% were deemed eligible and were accepted for waitlisting. Acceptance rates were not different between physician referrals and self-referrals (25% vs. 18%; p=ns). The main reasons for ineligibility were no indication (39%); contraindications (metabolic, 21%; medical comorbidity, 17%; psychosocial, 8%) or personal factors (15%).
Conclusions: Most referrals were received from people with diabetes, but acceptance rates were not significantly lower than for physician referrals. It will be important to increase awareness of severe hypoglycemia or glycemic lability as major indications for CIT among patients and physicians and to evaluate any impact this may have on the current acceptance rate of 19%.

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RÉSUMÉ

Objectifs : En raison de la disponibilité limitée des organes et des risques d'immunosuppression permanente, il est nécessaire de procéder à une sélection minutieuse au programme clinique de greffes de cellules d'îlots pancréatiques (PCGIP). Toutefois, bien que les indications de ce nouveau traitement demeurent incomprises, les critères de sélection ne cessent d'évoluer. Nous avons cherché à décrire le système d'aiguillage vers notre centre et les facteurs les plus fréquents dans la détermination de l'admissibilité au PCGIP.

Méthodes : Nous avons réalisé une revue rétrospective des dossiers de toutes les candidatures reçues au PCGIP de l'Université de l'Alberta entre mai 2009 et avril 2012. Nous avons extrait les données démographiques et cliniques ainsi que les sources d'aiguillage. Nous avons déterminé les résultats des candidatures et les raisons d'admissibilité ou d'inadmissibilité. Pour les sujets inadmissibles, nous avons noté la raison principale de l'inadmissibilité.

Résultats : Nous avons reçu 246 candidatures (âge moyen de 43 ans; étendue, de 13 à 78 ans; 54 % d'hommes) du Canada. La majorité (81 %) des aiguillages constituait des autoaiguillages, et le reste provenait des spécialistes (15 %) ou des médecins en soins primaires (4 %). Parmi les candidats, 19 % étaient considérés comme admissibles et admis à la liste d'attente. Les taux d'acceptation ne différaient pas entre les aiguillages provenant des médecins et les autoaiguillages (25 % *vs* 18 %; p=ns). Les raisons principales de l'inadmissibilité étaient les suivantes : absence d'indications (39 %); contre-indications (métaboliques, 21 %; comorbidité médicale, 17 %; psychosociales, 8 %); facteurs personnels (15 %).

Conclusions : La plupart des aiguillages provenaient de personnes diabétiques, mais les taux d'acceptation n'étaient pas significativement plus faibles que les aiguillages qui provenaient des médecins. Il faudra davantage sensibiliser les patients et les médecins sur le fait que l'hypoglycémie grave ou la labilité glycémique sont des indications majeures pour le PCGIP et évaluer les répercussions que cela peut avoir sur le taux d'acceptation actuel de 19 %.

Introduction

Canada has a long history of developing clinical islet transplantation (CIT) and, in 2000, this culminated in a report describing insulin independence in 7 of 7 CIT recipients (1). Now, 17 years since this original paper, we have learned that insulin independence is not maintained in all subjects. However, persistent graft function is seen in 80% of subjects at 5 years, albeit with small doses of supplemental insulin, with significant benefits of excellent glycemic control, stable blood glucose levels and protection from hypoglycemia (2–4). The benefits of islet transplantation and the potential for insulin independence have been extremely attractive to people with type 1 diabetes and their families. Health-care professionals may have been more cautious, recognizing the risks of lifelong immunosuppression.

Nevertheless, large numbers of applications have been received, and demand far outstrips the supply of organ donors. Generally, 2 islet infusions are required to achieve insulin independence, and not every pancreas processed yields sufficiently high-quality islets for transplantation (1), although with recent protocols, there has been up to 89.5% islet isolation success in some centres (5). Together with the risks for lifelong immunosuppression, it is, therefore, necessary to have an assessment procedure that can select subjects who will benefit most from CIT relative to the risks associated with the transplant procedure and immunosuppressant drugs. The indications and contraindications for CIT have been described previously and are summarized in Table 1. The assessment of the risk-benefit ratio should be individualized, but it would be time consuming to do it in person for all applicants. Our triage process has evolved with the goal of timely processing of applications prior to individual evaluation to select people with type 1 diabetes and severe hypoglycemia, hypoglycemic unawareness and/or glycemic lability despite optimal insulin management, for whom the risks of the procedure and lifelong immunosuppression are outweighed by the benefits of transplantation.

We sought to describe the acceptance rate for all applicants seeking CIT and to identify the most common factors that resulted in applicants being deemed eligible or ineligible for transplant by performing a retrospective review of applications to determine the main sources of referral and acceptance rates and the main reasons for ineligibility.

Methods

We conducted a retrospective chart review of all applications received by the Clinical Islet Transplant Program at the University of Alberta between May 2009 and April 2012. Each of these applications was assessed for source of referral, province of residence,

Table 1
Inclusion and exclusion criteria for clinical islet transplantation at the University of Alberta

Inclusion criteria	Exclusion criteria
Type 1 diabetes with >5 years of insulin use	Renal dysfunction: • eGFR ≤30 mL/mon/1.73^2 • Serum creatinine ≥200 μmol/L
Frequent, severe hypoglycemia (HYPO score ≥1047)	Active infection (TB, HIV)
Severe glycemic lability (lability index of ≥433 mmol/L^2/h/week)	Pregnancy, intent for future pregnancies or failure to follow effective birth control
Reduced hypoglycemia awareness (Clarke score ≥4)	Active malignancy
	Long-term anticoagulant use, thrombophilia or coagulopathy
	Significant coexisting disease with life expectancy <1 year
	Active substance abuse/smoking
	Not optimized glycemic regimen: • Taking ≤2 insulin shots/day • Self-monitoring of glucose ≤2 times/day
	Type 2 diabetes
	BMI >30 kg/m^2
	Age ≥75 or ≤18 years

BMI, body mass index; *eGFR,* estimated glomerular filtration rate; *HYPO,* hypoglycemia.
Note: See references 3 and 6.