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Clinical results of islet transplantation

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ABSTRACT

Islet transplantation is considered an advanced therapy in the treatment of type-1 diabetes, with a progressive improvement of clinical results as seen in the Collaborative Islet Transplant Registry (CITR) report. It is an accepted method for the stabilization of frequent hypoglycemia, or severe glycemic lability, in patients with hypoglycemic unawareness, poor diabetic control, or a resistance to intensive insulin-based therapies.

Worldwide data confirm a positive trend in this field, with the integrated management of pivotal factors: adequate islet mass, immunosuppressive protocols, additional anti-inflammatory therapy, and pre-transplant allo-immunity assessment.

Insulin independence has been observed in several clinical trials with different rate, ranging 100–65% of patients; the maintenance of this condition during the follow-up progressively decreased, actually arranged on 44% 3 years after the last infusion, according to data reported from the CITR.

Successful duration is progressively increasing, with ≥13 years being the longest reported insulin-free condition on record. The immediate results of functioning islet transplantation are an improvement in hypoglycemic awareness and a reduction in the glycated hemoglobin level. Furthermore, many studies have shown its influence on the chronic complications of diabetes, such as peripheral neuropathy, retinopathy, and macroangiopathy. Pre-transplant nephropathy remains an exclusion criterion as immunosuppressive therapy can exacerbate kidney-function deterioration. The problems linked to immunosuppression following islet transplantation for the treatment of type-1 diabetes need to be considered in order to achieve the correct risk/benefit ratio for each patient.

1. Introduction

Biological beta-cell replacement is the best rational approach in the treatment of type-1 diabetes (T1D).

Good glycemic control with intensive insulin treatment is known to markedly decrease the incidence of chronic microvascular complications and cardiovascular morbidity in patients with T1D [1,2]. However, this treatment is difficult, expensive, and associated with an increased incidence of severe hypoglycemia, which is often accompanied by hypoglycemic unawareness [3], provoking considerable morbidity and, at times, mortality [4].

In order to restore pancreatic endocrine function, islet infusion has optimal results with minimal risk. It is now an effective alternative choice to whole-pancreas transplantation in clinical practice, and not only in trials.

The evolution of the clinical outcome of islet transplantation took place during the last ten years following the experience of the Edmonton group, who transplanted islets alone in seven patients with T1D and obtained 100% insulin independence, a result that had never previously been achieved [5]. This trial became a milestone in the history of T1D therapy. Prior to this, islet transplantation was generally applied only when associated with kidney transplantation, and virtually never in clinical trials. Indications changed, and selection criteria were extended to include patients who did not need solid-organ transplant. Consequently, centers worldwide specifically dedicated their activity to islet transplantation in the clinical setting. Many protocols were developed with the aim to improve results linked to the various phases of the procedure, isolation, engraftment, and immunosuppression. Ten years after the proof-of-concept success of the Edmonton group, data published by the CITR, representing the most complete and standardized collection of information on islet transplantation in qualified centers, reported the efficacy and safety of outcome between 1999 and

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2010 [6]. The overall improvement of results is summarized by CITR data showing the global increase of the rate and duration of insulin independence. This success was the starting point for further studies on the multiple factors influencing islet transplantation, from the laboratory technique to the various immunosuppressive protocols. Insulin independence is not the only primary endpoint of islet transplantation. One of the most important problems of T1D is the management of hypoglycemia, particularly when sensibility has been lost: this is the first advantage achieved after islet transplantation, often without the achievement of insulin independence. Furthermore, the presence of endogenous insulin secretion, C-peptide, and the normalization of glycated hemoglobin levels are fundamental to control the chronic complications of T1D: microvascular [7], macrovascular [8], peripheral neuropathy [9], cerebral metabolism [10].

Encouraging results need to be counter-balanced with unsolved issues related to islet production, long-term transplanted tissue survival, and the risks of immunosuppression.

In this review, we analyze the current clinical data reported by the most active centers worldwide, and we also focus on unsolved problems and their possible solution.

2. Islet isolation

The first problem in the clinical application of islet transplantation is tissue availability.

The story of islet isolation is well known: in 1988, Camillo Ricordi introduced a technique to improve the efficiency of isolation techniques, which resulted in high islet yields [11]. This technique became the gold standard for all centers working on islets, both in research and in clinical application. Various studies have attempted to single out the donor and procedural factors needed for the success of pancreatic islet isolation and clinical transplantation [12–15]. The following donor variables have been identified: donor age, BMI, metabolic condition, pancreas characteristics, cause of death, and cold ischemia time. Various procedural evaluations have been performed on processing times, pancreas preservation methods, digestion enzyme selection, and purification methods. The most frequently used primary outcome in these studies pertained to islet yield represented by total islet equivalent (IEQ) and IEQ/g of pancreas or IEQ/kg of recipient body weight. Recently, the CITR group reported a comprehensive analysis of clinical grade islet products from a total of 1017 isolations performed at CITR-participating North American, European and Australian centers [16]. They found a significant IEQ increase in those most recently infused, and that a higher transplanted islet mass was independently associated with the clinical outcome of the insulin independence rate. As regards the endless debate concerning collagenase, they observed clear yield differentiation with Liberase and NB1 that were negatively and positively correlated with the IEQ/particle ratio, respectively. No direct correlation between donor age and IEQ-based measures was found. The CITR database provided information on donor insulin treatment, which had not previously been considered as a clinical islet isolation variable. Correlation was found between insulin use and higher beta cell/kg recipient. This finding is supported by preclinical research, which suggests that insulin treatment can promote or maintain islet beta-cell mass in rodents [17,18].

3. Indications for islet transplantation

The indications for islet rather than whole-pancreas transplantation in patients undergoing simultaneous or later kidney transplantation are well documented. They include: recipient suffers from major cardiovascular disease; when simultaneous whole-pancreas/kidney transplantation is considered too risky; the risk of re-transplantation when a pancreas is lost after simultaneous pancreas/kidney transplantation; the surgical unsuitability of a pancreas from a kidney donor; the recipient subsequently opts out of whole-pancreas transplantation. For patients that need immunosuppressive therapy, islet transplantation might improve glycemic control, with beneficial effects on both patient and graft survival [19].

The indications concerning islet transplantation alone (ITA) are based on the clinical data produced by pancreas transplantation. In 2006 the American Diabetes Association stated the following specific criteria for pancreas and islet transplantation: (1) a history of frequent, acute, and severe metabolic complications (hypoglycemia, marked hyperglycemia, ketoacidosis) requiring medical attention; (2) clinical and emotional problems with exogenous insulin therapy that are so severe as to be incapacitating; and (3) consistent failure of insulin-based management to prevent acute complications [20]. All centers with great experience in ITA underline the importance of hypoglycemic unawareness, which is one of the most dangerous complications of intensive insulin therapy and is considered the main criteria of patients eligibility for islet transplantation. It is has been shown that severe hypoglycemia depends mainly on the absence of residual insulin secretion, regardless of treatment intensity [21], and that the risk of death at five years is increased 3.4-fold in diabetic patients who report severe hypoglycemia [22].

Exclusion criteria are similar to those for all types of transplant, particularly chronic infective disease, a history of cancer, and psychiatric diseases.

4. Islet transplant procedure

The standard method for islet transplantation is intraportal infusion through percutaneous catheterization of a peripheral portal branch with ultrasound guidance, or by surgical catheterization of a small mesenteric vein. The combined ultrasound and fluoroscopy-guided technique is considered the safest procedural method, with a low complication rate [23].

Two/three islet infusions from multiple donors are typically required for each transplanted patient, although many recent trials have focused on the possibility of a single infusion.

New perspectives in identifying alternative sites for islet infusion were provided in a pilot study, where the feasibility and safety of bone marrow were demonstrated in four patients who underwent islet autotransplantation after total pancreatectomy [24].

5. Results of clinical trials

To understand the volume of islet transplant activity, we have to refer to CITR reports (Fig. 1). Islet transplant clinical activity data have been collected since 1999 by the CITR, supported by the Juvenile Diabetes Research Foundation (JDRF), using results from the USA, Canada, and several centers in Europe and Australia comprising 81% of all allogeneic islet transplants conducted as clinical trials or standard of care. Six hundred seventy-seven recipients of allogeneic islet transplantation, 575 islets alone, 110 islets with kidney, were reported in 2010 [6].

5.1. Metabolic data

In all studies, function of the transplanted islets is studied in terms of: C-peptide secretion (basal and after stimulus), glycated hemoglobin values, and insulin independence. Following transplantation, the absence of further episodes of hypoglycemic unawareness is always reported, and is included in the primary