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Review

Treating diabetes with islet transplantation: Lessons from the past decade in Lille

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Abstract

Type 1 diabetes (T1D) is due to the loss of both beta-cell insulin secretion and glucose sensing, leading to glucose variability and a lack of predictability, a daily issue for patients. Guidelines for the treatment of T1D have become stricter as results from the Diabetes Control and Complications Trial (DCCT) demonstrated the close relationship between microangiopathy and HbA1c levels. In this regard, glucometers, ambulatory continuous glucose monitoring, and subcutaneous and intraperitoneal pumps have been major developments in the management of glucose imbalance. Besides this technological approach, islet transplantation (IT) has emerged as an acceptable safe procedure with results that continue to improve. Research in the last decade of the 20th century focused on the feasibility of islet isolation and transplantation and, since 2000, the success and reproducibility of the Edmonton protocol have been proven, and the mid-term (5-year) benefit–risk ratio evaluated. Currently, a 5-year 50% rate of insulin independence can be expected, with stabilization of microangiopathy and macroangiopathy, but the possible side-effects of immunosuppressants, limited availability of islets and still limited duration of insulin independence restrict the procedure to cases of brittle diabetes in patients who are not overweight or have no associated insulin resistance. However, various prognostic factors have been identified that may extend islet graft survival and reduce the number of islet injections required; these include graft quality, autoimmunity, immunosuppressant regimen and non-specific inflammatory reactions. Finally, alternative injection sites and unlimited sources of islets are likely to make IT a routine procedure in the future.

Keywords: Islet transplantation; Diabetes cell therapy; Beta score; Brittle diabetes; Type 1 diabetes

1. Introduction

The Diabetes Control and Complications Trial (DCCT) demonstrated the close relationship between microangiopathy and HbA_{1c} levels, and provided evidence of the beneficial effects of improving glycaemic control. However, achieving a good HbA_{1c} level is not so simple, as lowering blood sugar carries a risk of hypoglycaemia. Indeed, type 1 diabetes (T1D) is due to the loss of both beta-cell glucose sensing and insulin secretion, leading to glucose variability and a lack of predictability, both of which are daily issues for patients with T1D and their physicians. Many methods have been developed to improve glycaemic control, including the use of devices such as glucometers, ambulatory continuous glucose monitoring, and subcutaneous and intraperitoneal pumps. In addition to these technological approaches, islet transplantation (IT) has emerged as an acceptable safe procedure with results that continue to improve. The feasibility of islet isolation and transplantation were demonstrated in the last decade of the 20th century and, since 2000, reproducibility of the Edmonton protocol has been proven and the mid-term (5-year) benefit–risk ratio evaluated. This report covers the current state of diabetes cell therapy as well as its future prospects.

2. The "feasibility" period: from 1993 to 2000

After the first attempts at IT in rodents in the 1970s, immunosuppression as a result of kidney transplantation was used to conduct simultaneous allogeneic islet and kidney or islet after kidney (IAK) transplantation. However, in contrast to autotransplantation, allotransplants resulted in a low rate of insulin independence at 1 year (< 10%) that was related to recurrence of allo- and autoimmunity and the diabetogenic effect of immunosuppressant drugs. Also, despite standardization of islet isolation, islet cells from a single donor were not quantitatively sufficient to achieve insulin independence, and the use of cryopreserved islets was a failure. This led to an approach using sequential transplantation of islet cells isolated from two or three successive donors [1] to increase the transplanted islet mass and compensate for the post-transplantation destruction of islets.

In the early days, islets were infused over 12 days through a percutaneous intraportal catheter implanted surgically at the time of the first islet injection; the catheter was maintained with heparin until > 8000 islet equivalents (IEQ) per kg body weight had been transplanted. The immunosuppressive regimen was determined by kidney transplantation and consisted of antilymphocyte serum for induction, and cyclosporine, steroids and mycophenolate for maintenance. Three patients transplanted according to this procedure (before 2000) had a post-transplantation C-peptide range of 3–5 ng/mL, which unfortunately fell to < 0.2 ng/mL within 3 months of transplantation [1,2]. This failure was probably related to the effects of the large steroid doses used for kidney transplants on autoimmunity. No kidney graft loss, however, was observed.

Soon after this, modification of immunosuppression led to the first clinical success of islet cell transplantation in non-kidney-transplanted T1D patients in Edmonton, Canada, in 2000 [3].

3. The Edmonton protocol and its reproducibility (2000–2008)

The strategy of the Edmonton group was to dissociate IT from kidney transplants. The immunosuppressive regimen was justified by the life-threatening brittle diabetic state with hypoglycaemia unawareness, while the surgical risk was minimized by the transplantation of only the endocrine portion of the pancreas and not the whole organ. The "Edmonton protocol", which uses a steroid-free combination of low-dose tacrolimus and a new immunosuppressive agent, sirolimus, a mammalian target of rapamycin (mTOR) inhibitor, dramatically improved IT prognosis [4]: insulin independence was observed in 100% of the first seven transplanted patients [3] and 80% still had detectable peptides 5 years later [4].