Islet transplantation: cell therapy for type 1 diabetes

Antoine Buemi

Islet transplantation holds great promise for the treatment of type 1 diabetes (T1DM), as it offers the potential to restore euglycaemia in a reliable manner, protects against hypoglycaemia and glycaemic lability in a way that exogenous insulin administration has thus far been unable to achieve, and is associated with far fewer risks than whole-pancreas transplantation. Moreover, for patients requiring total pancreatectomy for benign disease, isolation of islets from the diseased pancreas with intrahepatic transplantation of autologous islets can prevent or ameliorate postsurgical diabetes and improve quality of life. We, therefore, seek to add this alternative treatment to the therapeutic modalities proposed within our institution.

La transplantation d'îlots de Langerhans : une thérapie cellulaire pour le diabète de type 1

La transplantation d'îlots de Langerhans est très prometteuse pour le traitement du DT1, car elle offre la possibilité de rétablir l'euglycémie de manière fiable, protège contre l'hypoglycémie et la labilité glycémique d'une manière que l'administration d'insuline exogène n'a pas pu atteindre jusqu'à présent et est associée à beaucoup moins de risques que la transplantation du pancréas entier. De plus, pour les patients nécessitant une pancréatectomie totale pour une maladie bénigne, l'isolement d'îlots de Langerhans à partir du pancréas malade avec une transplantation intra-hépatique d'îlots autologues peut prévenir ou améliorer le diabète post-chirurgical et améliorer la qualité de vie. Notre objectif est d'ajouter ce traitement alternatif dans notre institution.

KEY WORDS

Îlots de Langerhans, transplantation, diabète de type 1

INTRODUCTION

Human pancreatic islet isolation and transplantation techniques have transitioned from a rare, experimental and only occasionally successful procedure to a routine clinical procedure with predictable efficacy for selected patients with type 1 diabetes mellitus (T1DM).

The treatment is offered only for selected patients with unstable T1DM and hypoglycaemia unawareness, severe hypoglycaemic episodes and glycaemic lability who cannot be stabilized successfully with intensive insulin, pumps and/or continuous glucose monitoring therapies.

Accelerated progress has occurred in the past two decades in both the number of human islet transplantations performed and the long-term clinical outcome success. This minimally invasive procedure can now routinely result in longterm glycaemic control with near normalization of HbA1c in the absence of severe hypoglycaemic episodes (1,2).

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MOTS-CLÉS ▶ Islet transplantation, Islet auto-transplantation, type 1 diabetes

Since 1974, the year of the first islet transplantation, the rate of insulin independence at one year in transplanted patients with insulin-independent diabetes has increased from 8% to more than 50% (3).

Numerous international studies have also shown that islet transplantation allows:

- improve the quality of life, whether the patient is weaned from exogenous insulin therapy.
- stabilize diabetes, by maintaining an HbA1c of at least less than 7% and by avoiding severe hypoglycemia events.
- reduce the risk of progression of diabetic vascular complications in the medium term by achieving better metabolic control of diabetes.
- for kidney transplant patients, to obtain a better survival of the renal graft by avoiding the recurrence of diabetic nephropathy on the transplanted organ (4).

INDICATIONS FOR ISLET TRANSPLANTATION

ISLET TRANSPLANT ALONE

The major indications for islet transplant alone are T1DM (C-peptide negative) complicated by hypoglycaemia unawareness, severe hypoglycaemic episodes and/or glycaemic lability, despite corrective attempts to implement intensive insulin treatment and appropriate monitoring, under the supervision of a diabetologist or endocrinologist.

Inclusion criteria comprise a duration of T1DM >5 years and age >18 years to avoid exposure to the risks of immunosuppression in paediatric patients. A possible exception to this age limit could be considered in selected patients in whom the risk of death or irreversible brain injury from severe hypoglycaemic episodes cannot be avoided by alternative strategies or interventions. Patients with a high BMI (>30 kg/m2) and/or of weight >90 kg and/or daily insulin requirement >1.0 U/kg should be avoided, to exclude those with marked insulin resistance or excessively high insulin requirements (5).

ISLET AFTER KIDNEY (IAK) AND SIMULTANEOUS ISLET-KIDNEY (SIK)

Patient selection for IAK ans SIK transplantation is less stringent than for islet transplant alone, as patients are already being treated with chronic immunosuppression because of the previous kidney transplant. Good function of the transplanted kidney should be documented before considering prospective recipients. Moreover, a risk of broad sensitization to HLA might ex ist after blood transfusions or a kidney graft. A negative prospective cytologic crossmatch, or at least avoidance of previous sensitized antigens, becomes mandatory for the future successful maintenance of an islet transplant (4).

ISLET AUTOTRANSPLANTATION

Surgical diabetes, caused by extensive pancreatic resection, is a condition comparable in severity to T1D. Chronic pancreatitis is the most frequent indication for extensive pancreatic resection in adults or children with "rare" pancreatic disease. Extensive pancreatic resection is often necessary in patients with intractable pain in the setting of chronic pancreatitis, and islet autotransplantation is emerging as a solution to prevent surgical diabetes (7).

ISLET ISOLATION AND TRANSPLANTATION

CLINICAL ISLET ISOLATION, PURIFICATION AND PRE-TRANSPLANT CULTURE

Human islet isolation and purification requires a 5–7 h multi-step process to extract the small islet fraction, which represents hundreds of thousands of cell clusters comprising only 1–2% of the total pancreatic tissue volume. Enzymatic digestion, controlled gentle mechanical shear, purification and culture is the established approach to preparation of a final enriched islet cell product in <5 cm3 of tissue pellet, which is considered safe for intra-portal infusion. Greater than 5,000 islet equivalents (IEQ) per kg of the recipient body weight is generally recommended as the minimal β-cell mass required to observe a notable metabolic effect following transplantation. However, islet products obtained from single donor pancreases are more likely to yield insulin independence following transplantation if the final cell product contains >7,000 IEQ/kg (5). The development of the Automated Method (using the Ricordi Chamber and a continuous digestion-filtration pancreas processing method (8)) paralleled a substantial qualitative and quantitative improvement in the human pancreatic islet products available for transplantation, which enabled the initial success reported in early pilot clinical trials. The main procedural steps in pancreas digestion and islet purification include

disassembling the pancreas through a mechanically enhanced, continuous flow, enzymatic digestion process, following intraductal pancreatic perfusion with a solution containing enzyme blends (collagenase type I and type II and selected proteases) followed by centrifugal density gradient purification. The final islet preparation is placed in culture media and incubated for 24–72 h, to enable quality controls for product release assessment to be performed, as well as the initiation of induction immunosuppressive treatment in the recipient before they receive the transplant. In addition, a period of islet culture leads to increased purification, with minimization of dead or apoptotic cells and their by products, which could trigger and/or increase nonspecific inflammation after the transplantation, thus reducing exposure of newly transplanted islets to harmful cytokines (5).

INTRAPORTAL ISLET TRANSPLANTATION

The final islet-cell product is suspended in transplant media and loaded in a sterile infusion bag with 70 units heparin per kg recipient body weight, and infused by gravity following percutaneous catheterization of the portal vein.

The portal vein can be accessed easily by interventional radiology, through a minimally invasive percutaneous transhepatic approach under ultrasonographic and fluoroscopic guidance, making islet transplantation (in expert hands) one of the safest and most simple transplant procedures. An open surgical technique has been advocated when percutaneous access is not possible (for example, in instances of large hepatic haemangioma or lack of local radiological expertise). In these cases, the portal system can be accessed surgically using a minimally invasive approach by recanalization of the obliterated left umbilical vein to enable access to the left portal system, or by limited laparotomy with intravenous delivery of the islet-cell product following catheterization of an omental or mesenteric vein (5,9).

RECIPIENT IMMUNOSUPPRESSION

Effective control of both alloimmune and autoimmune islet attack in the recipient remains the cornerstone of posttransplant islet recipient treatment. Unfortunately, many of the compounds used are toxic to the islets themselves. This is especially true of corticosteroids that formed the backbone of islet transplant immunosuppression before the Edmonton Protocol. One of the main strengths of the Edmonton Protocol report was its avoidance of corticosteroid use. In its place, sirolimus (a macrolide antibiotic which inhibits mTOR) and tacrolimus (a calcineurin inhibitor) were used (10). These are not without their own side effects as tacrolimus can cause neuro- and nephrotoxicity in addition to β-cell damage. The choice to eliminate tacrolimus and/or sirolimus may improve metabolic function but may be detrimental when considering the risk of rejection. Mycophenolate mofetil (CellCept), a purine biosynthesis inhibitor, is now more commonly used either in combination with tacrolimus or sirolimus. Induction therapy is used in most islet transplant protocols. The Edmonton Protocol used daclizumab, an anti-interleukin 2 receptor monoclonal antibody (anti-CD25) given pretransplant and for four doses biweekly posttransplant. Thymoglobulin (also known as rabbit antithymocyte globulin or ATG) was promoted by Hering and colleagues in combination with etanercept. Since then, the same group reported that initial T-cell depletion therapy has a considerable positive effect on long-term insulin independence irrespective of the choice of maintenance immunosuppression (5).

RISKS OF ISLET TRANSPLANTATION

One of the attractions of islet transplantation is the reliability and safety of the intrahepatic percutaneous transhepatic portal vein approach. Bleeding and portal venous thrombosis remain potential risks of intrahepatic islet transplantation. Nevertheless, the risk of both procedure-related complications can be minimized by close adherence to protocols for heparinization and obliteration of the catheter tract (11).

The most frequent complication of islet transplantation is a transient discomfort or occasional modest pain at the site where the intrahepatic catheter is inserted. Standard analgesic medications can be administered easily with full resolution within 24–48 h in most cases. Another risk following intraportal islet transplantation is transient mild increases in levels of alanine transaminase and aspartate transaminase that occur in up to half of patients, but usually normalize completely by 1 month without intervention.

Concerning the potential risk of malignancies from chronic immunosuppression, treatable skin basal or squamous cell carcinoma were reported in 17 of 864 patients, with an overall rate of 2%. (12).

CONCLUSION

Islet transplantation is a great opportunity for a subset of patients with frequent, severe hypoglycemia and/or glycemic lability, and can provide the ability to achieve both excellent glycemic control and freedom from hypoglycemia even if insulin independence is not maintained.

Our goal is to make this procedure a reality in our Institution by profiting from our multidisciplinary expertise, our modern infrastructure, and the ever-increasing demand from many patients and to be able to make our contribution striving to further refine and enhance islet transplantation until the elusive goal of a cure for diabetes is reached.

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CORRESPONDANCE

DR ANTOINE BUEMI MD
Cliniques universitaires Saint-Luc
Service de chirurgie et transplantation abdominale
Avenue Hippocrate 10
B-1200 Bruxelles, Belgique