Who should benefit from diabetes cell therapy?

Qui peut tirer bénéfice d’une thérapie cellulaire du diabète ?

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Résumé
Le diabète de type 1 est une condition éminemment instable en raison de la double perte de l’insulino-sécrétion et de la sensibilité au glucose. Les recommandations concernant son traitement sont devenues plus strictes depuis que les résultats du DCCT ont démontré l’existence d’une relation entre microangiopathie et HbA1c ou moyenne glycémique d’une part, tandis que, d’autre part, le rôle délétère de la variabilité du glucose sur la macroangiopathie était plus récemment suspecté. Les stratégies thérapeutiques requièrent d’abord la prise en charge des causes organiques d’instabilité chaque fois que possible, puis l’optimisation de l’insulinothérapie par utilisation d’analogues, d’injections multiples, voire d’une insulinothérapie sous-cutanée continue ambulatoire en pompe. Des alternatives plus sophistiquées sont parfois nécessaires dans les formes les plus instables, dont la transplantation d’îlots. Nous proposons la transplantation d’îlots après rein chez les patients diabétiques insuffisant rénaux inéligibles pour une double transplantation rein-pancréas (par exemple, chez les patients « C peptide négatifs » de plus de 45 ans ou avec des complications macroangiopathiques sévères) si la créatininémie est stable en-dessous de 20 mg/l au moins six mois après la transplantation rénale et après l’arrêt de la corticothérapie. La transplantation d’îlots seuls est proposée à (1) des patients diabétiques C peptide négatifs, (2) âgés de 18 à 65 ans avec une durée de diabète d’au moins cinq ans, (3) traités par insulinothérapie intensive sous-cutanée, mais incapables d’obtenir une hémoglobine glyquée inférieure à 7 % sans hypoglycémies et/ou présentant une instabilité avec des hyper- ou des hypoglycémies imprévisibles altérant la qualité de vie, (4) avec un poids corporel normal (<80 kg) et/ou des besoins quotidiens en insuline bas (le plus bas étant le mieux), (5) avec une fonction rénale proche de la normale (clairance de la créatinine supérieure à 60 ml/min avec albuminurie inférieure à 300 mg/24 h), (6) sans désir de grossesse chez les femmes. Actuellement et jusqu’à plus complète évaluation du rapport bénéfice–risque à cinq ans, la transplantation d’îlots demeure du domaine de la recherche clinique. Comme cela a été le cas pour les autres types de transplantation, et une fois que la greffe d’îlots aura été reconnue comme une procédure de routine, la priorité des patients sur liste pourra être assistée par le calcul d’un score qui devrait être déterminé par une équipe multidisciplinaire.

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Mots clés : Greffe d’îlots ; Thérapie cellulaire du diabète ; Indications

Abstract
Type 1 diabetes are intrinsically unstable conditions because of the loss of both insulin secretion and glucose sensing. Guidelines to treat type 1 diabetes have become stricter since the Diabetes Control and Complications Trial (DCCT) results demonstrated the close relationship between microangiopathy and HbA1c levels, whereas the deleterious role of glucose variability on macroangiopathy has been more recently suspected. Therapeutic strategies first require the treatment of underlying organic causes of the brittleness whenever possible and, secondly, the optimization of insulin therapy using analogues, multiple injections and consideration of continuous subcutaneous insulin infusion. Alternative approaches may still be needed for the most severely affected patients, including islet transplantation. We propose islet after kidney transplantation in diabetic patients with end-stage kidney disease ineligible for double kidney-pancreas transplantation (i.e C peptide negative patients over 45 years of age or with severe macroangiopathy) if creatinine blood levels are stable below 20 mg/l at least six months after kidney transplantation and steroid discontinuation. Islet transplantation alone is proposed to (1) C peptide negative diabetic patients, (2) aged 18–65 with a duration of diabetes of at least five years, (3) treated with intensive subcutaneous insulin therapy, but unable to obtain a glycated hemoglobin level below 7% without hypoglycemia and / or with brittleness and unpredictable hyper- and hypoglycemia altering quality of life, (4) with normal body weight (<80 kg)

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1. Introduction

The transplantation of pancreatic β-islets requires significant organization relying on pancreas harvesting in a donor in association with the French Agency of Biomedicine and the isolation of β-cells in an authorized laboratory. The infusion of β-cells is performed either by percutaneous or surgical route and requires immunosuppression.

In France, diabetes cell therapy is organized in two networks: the first one, named G4, groups Lille, Amiens, Caen, Rouen, and Reims with an isolation and transplantation centre in Lille (Unit INSERM U 859); the other one, named GRAGIL, reunites most of the Eastern university hospitals of France with an isolation centre located in Geneva, Switzerland and soon in Grenoble, France, and implantation centres in each university hospital of the network. A third isolation lab should soon be started at the St. Louis hospital in Paris.

In a type 1 diabetic patient for whom optimized insulin therapy with multiple injections or an ambulatory pump has failed, two alternatives are possible:

- a technical solution with an external or implantable pump associated with an ambulatory continuous blood glucose monitoring system and possibly an adaptable program of insulin delivery;
- a biological solution with the transplantation of either a whole pancreas or isolated islet β-cells

The criteria for choosing between these different therapeutic options are not yet very well defined.

The goal of this article is:

- to review islet transplantation taking into account the knowledge about unbalanced diabetes as well as the success rates and the side effects of islet transplantation in comparison with other techniques;
- to more precisely determine the indications according to exclusion criteria, relying most of the time on common sense, in islet transplantation alone or after kidney graft.

2. Diabetes cell therapy in 2009

In 2000, the Edmonton group published in the New England Journal of Medicine the results of islet transplantation in seven patients suffering from type 1 diabetes. This treatment was proposed for patients with severe recurrent hypoglycemic episodes or such a lability that the risks of transplantation and immunosuppression were judged to be lower than those of an unsteady diabetes [1].

2.1. Risks of a poor metabolic control in a diabetic patient

The risks of poor glycemic imbalance are well identified both on the macro- and microangiopathic levels, whereas the benefits of good blood glucose control have been perfectly demonstrated in the DCCT study [2,3]. In the 1990s, another form of diabetes was identified qualified as brittle due to unpredictable blood glucose variability that was severe enough to induce a poor quality of life (QOL) with frequent or long hospitalizations.

Those labile diabetes were associated with lower QOL scores, more severe microangiopathic and gestational complications (46% versus 7% in more stable forms of diabetes) and a higher risk of death (19% at 10 years) mainly linked to hypoglycemia, ketoacidosis episodes and renal failure. In cases of associated dysautonomy, the mortality rate could reach 50% at five years [4].

The definition of brittleness includes a certain degree of subjectivity and depends on the tools used to assess it [5]. Every case of unstable diabetes requires a search for an etiology and more specifically malabsorption (steatorrhea, celiac disease), adrenal failure or a dysautonomic neuropathy.

Nevertheless, despite therapeutic advances, hypoglycemia remains an unresolved pitfall when looking for an optimal blood glucose imbalance in type 1 diabetes [6]. Despite the ongoing debate, the cognitive consequences of a poor glycemic imbalance have been demonstrated by morphological techniques showing microstructural anomalies of the white substance correlated with lower performances in neurocognitive testing, and with diabetes duration and glycated hemoglobin increase [7].

2.2. Islet transplantation benefit–risk ratio

2.2.1. Benefits

On the one hand, the benefits of islet transplantation depend on its success rate and, on the other hand, the side effects of islet injection and long-term immunosuppression.

The success of islet transplantation can be defined with four main criteria: disappearance of hypoglycemia episodes; insulin discontinuation; HbA1c long-term normalization; and a more technical composite score, the β-score, taking into account the value of fasting blood glucose, glycated hemoglobin, stimulated C peptide and anti-diabetic treatment.

Ryan et al. have shown that the first benefit of islet transplantation corresponded to hypoglycemia disappearance,
demonstrated by the Hyposcore, that takes into account the frequency and severity along with lack of perception of hypoglycemia [8]. The International Collaborative Transplantation Registry (CITR), which includes more than 300 islet-transplanted patients in North America and Europe, also confirms the improvement in hypoglycemia episodes in transplanted patients, at least during insulin-independency [9].

According to the CITR registry, the frequency of insulin-independence after islet transplantation alone when all centres are taken into account is 55% at one year and 35% at two years. The most experimented centres have a rate of insulin-independence at two years with normal HbA1c levels around 60% whereas this rate is about 45% at three years. In Lille, the rate of insulin-independence with HbA1c levels inferior to 6.5% is 71% at one year and 57% at two years. When patients are divided into two groups according to their β-score, one month after the last cell-infusion, the group with a β-score greater than 6 has a longer duration of insulin-independence, emphasizing the importance to transplant both a satisfying qualitative and quantitative graft. [10]. This point is important to consider since for the diabetologist as for the patient, taking into account the investment and the risk represented by the injection of two to three cell preparations, it is of the utmost importance to determine the long-term prognostic factors to obtain a significant insulin-independence duration with normal HbA1c levels. Moreover, this probably conditions the evolution of complications.

Concerning islet after kidney transplantation, 46 patients are registered in the CITR (versus 279 for islet transplantation alone). Eleven of the patients come from Lille with an insulin-independence rate with HbA1c levels inferior to 6.5% of 54% at one year, increasing to 72% if a less strict level of HbA1c (<7%) is considered.

2.2.2. Side effects

Cell diabetes therapy induces a certain number of side effects, mainly related to the islet injection procedure and immunosuppression [11]. In the CITR, frequency of side effects the first year post-transplantation is assessed at 0.71 event / person / year associated with the infusion and 0.87 event / person / year associated with immunosuppression. The number of side effects then decreases to less than 0.21 event / person / year [8]. In our experience, the overall frequency of side effects was 0.9 event / person / year.

The other complications underlined by different authors correspond to the occurrence of anti-HLA antibodies (sensitization), particularly when immunosuppressive drugs are discontinued in patients who have lost their graft [12–14]. The evolution of these antibodies and their consequences for the present islet graft prognosis as well as for a possible future transplantation, especially a kidney graft, remain to be determined.

Immunosuppressive treatment also favours the occurrence of metabolic complications such as dyslipidemia (40 to 80%) and hypertension (30 to 40%), generally easily treated with the usual course of drugs, though taking into account that certain drugs should be avoided due to possible interferences with the metabolism of immunosuppressive medications. Finally, Senior et al. have emphasized the existence of a slight deterioration of glomerular filtration, especially in women of low body-weight who have already had microangiopathic complications [15]. Nevertheless, their study did not include a control group, and more recent data with a control group do not confirm these deleterious effects [16,17].

2.3. Comparison of the results of islet transplantation with other techniques

2.3.1. Comparison of islet transplantation with optimized insulin therapy [17]

In a prospective cross-over cohort in patients receiving at least 12 000 islet-equivalent per kilo with an immunosuppressive regimen including anti-lymphocyte serum, tacrolimus and mycophenolate, Warnock et al. compared the evolution of HbA1c levels, glomerular filtration rates, retinopathy and neuropathy three years after intensive insulin therapy (n = 42) or islet transplantation (n = 31). HbA1c levels were significantly better three years after transplantation in the transplanted group with a lower decrease in the slope of glomerular filtration rate compared to the intensively treated group and a lower occurrence of eye events. However, there was no difference in terms of neuropathy assessed by nerve conduction velocity, in contrast with Del Carro’s findings [18] in islet- after kidney-transplanted patients or with Lille’s group that found a significant improvement of nerve conduction velocity in 50% of islet-alone or after kidney-transplanted patients who suffered from a neuropathy before transplantation [19].

2.3.2. Comparison of implantable pump and islet transplantation [20]

In a non randomized study using a historical control group treated with an implantable pump, the mean HbA1c level, daily insulin needs and number of hypoglycemia episodes were significantly lower in the “islet-transplanted” versus the “pump” group at 12 months, whereas after 24 and 36 months, mean daily insulin needs, HbA1c, and frequency of hypoglycemia episodes remained significantly lower in the “islet-transplanted” group versus baseline, and mean HbA1c and daily insulin needs versus the “pump” group. Adverse events were, however, four times more frequent with islet transplantation than with implantable pump, though their numbers decreased over time. Nevertheless, no death, thrombosis or kidney graft loss were observed in this study.

2.3.3. Comparison of islet after kidney and combined kidney-whole pancreas transplantation [21]

Gerber et al. compared a group of 13 islet after kidney-transplanted patients and 25 patients treated with double kidney-whole pancreas transplantation three years after transplantation.

The mean HbA1c levels were not different between the two groups, despite a higher frequency of insulin-independence (96% versus 31%) in the “double kidney-whole pancreas” transplantation group compared to islet and kidney transplantation.
Kidney function remained identical, but the double kidney–pancreas transplantation was associated with a significantly higher rate of side effects, 40% of relaparatomies in particular.

3. Conclusion

Finally, in 2009, islet transplantation helps reach a rate of insulin-independence with HbA1c lower than 6.5% fluctuating between:

- fifty and 80% one year after the transplantation;
- thirty and 60% two years later.

According to the CITR, the factors favorably influencing islet transplantation prognosis are a high number of infusions and transplanted islet equivalent, a low level of pretransplantation HbA1c levels, an isolation lab associated with a transplantation centre and the use of daclizumab and etanercept (an anti-TNF alpha) for induction.

The islet transplantation allows for better metabolic control than implantable pump or optimized insulin therapy at the cost of a higher rate of side effects.

The one-year results are similar between islet and whole pancreas transplantation even if pancreas transplantation helps obtain a longer duration of insulin independence, but at the cost of a higher rate of side effects, particularly a mortality risk of 2%.

Otherwise, islet transplantation has shown favorable effects on the occurrence of retinopathic complications [22] and on improvement of neuropathy. Further studies are nevertheless necessary in terms of nephropathy and sensitization.

4. When to consider islet transplantation in a type 1 diabetic patient?

The indication of islet transplantation in a type 1 diabetic patient relies on a few rules of common sense leading to the exclusion of patients who are at high risk of complications related to the injection procedure or to the immunosuppressive treatment. It is thus logical to consider islet transplantation in already immunosuppressed patients, especially in kidney-transplanted patients. Finally, islet transplantation alone should be discussed according to the benefit–risk ratio for each patient.

4.1. Common sense contra-indications

Diabetes cell therapy remains a treatment given in the framework of clinical research in most countries, including France. A certain number of exclusion criteria are retained by most cell therapy centres and have been validated by the Food and Drug Administration. The most important are:

- a detectable blood C peptide level which would not allow the assessment of graft results;
- a blood HbA1c level greater than 12%, usually indicating a patient’s general neglect of his diabetes, which often indicates a high possibility of poor adherence to the constraints of a future islet transplantation;
- a BMI greater than 28 kg/m² (30 in some centres) or a high level of insulin need (globally greater than 1 U/kg per day) are also contra-indications that make it impossible to obtain insulin independence with two or three islet cell preps in these patients;
- the progressive complications of diabetes such as an untreated progressive coronaropathy, an unstabilized retinopathy, proteinuria greater than 0.3 g/24 h, blood creatinine levels greater than 16 mg/l or creatinine clearance inferior to 60–70 ml/min, all constitute contra-indications to islet cell transplantation;
- patients presenting an increased risk of complications related to immunosuppression due to:
  - untreated hyperlipidemia (generally speaking an LDL cholesterol level > 130 mg/dl),
  - blood pressure greater than 160/100 mmHg,
  - chronic infection especially by C and B hepatitis viruses,
  - progressive neoplasia except for basocellular skin cancers or in situ cervical gynecological cancers.
- patients presenting an increased risk of complications linked to islet infusion due to liver alterations (especially a 3-fold increase in liver enzymes, cholestasis, angiomia, etc.);
- the existence of anti-HLA antibodies at a rate greater than 20% before transplantation since these antibodies make it more difficult to identify a compatible donor, whereas the failure of the graft could favor sensitization;
- patients receiving systemic steroids;
- young women who wish to become pregnant.

4.2. Islet transplantation in patients with kidney transplantation [23–26]

Islet transplantation in the kidney-transplanted patient either simultaneously or after kidney transplant can be proposed in type 1 diabetic patients with an undetectable C peptide level, a body-weight globally lower than 80 kg (BMI < 28) when these patients are ineligible for a double pancreas-kidney transplantation, which remains the reference treatment. Ineligibility relies generally on an age greater than 45 years and/or severe macroangiopathic complications. The absence of sensitization should be checked.

Patients who have previously received a double kidney/pancreas transplantation with a secondary loss of the pancreatic graft but the kidney graft remains functional, could also benefit from an islet after kidney transplantation.

To consider islet after kidney transplantation, kidney function should be stable, inferior to 20 mg/l. If considering the use of the Edmonton protocol, a progressive steroid weaning in the six months following the kidney transplantation should be considered, in the absence of an acute rejection episode. This period is used to progressively introduce sirolimus. Nevertheless, the immunosuppressive regimen is variable depending on the medical staff’s treatment protocol and low dose steroids are sometimes maintained in higher risk patients to avoid acute kidney rejection. When an immunocconversion is scheduled, it is important to consider a relatively short time (< 2 years after the
kidney graft) in a patient with well-controlled blood pressure, no significant proteinuria and with no history of acute rejection.

4.3. Islet alone transplantation [27]

The most difficult situation is in the indication of islet transplantation in diabetic patients who can be offered three alternatives:

- optimized insulin therapy with a pump coupled with continuous blood glucose monitoring with its psychological repercussion and long-term acceptance problems;
- islet transplantation with its side effects linked to the immunosuppressive treatment and the pitfall of long-term maintenance of insulin-independence;
- a third alternative, not very often proposed until now given the relatively high morbimortality rate is an isolated whole pancreas transplantation.

Inclusion criteria in an islet cell transplantation protocol are for patients:

- suffering from type 1 diabetes for at least five years;
- aged 18 to 65;
- with an undetectable stimulated blood C peptide level.

The best indication corresponds to patients presenting severe non-felt hypoglycemia episodes and / or brittleness despite intensive diabetes treatment by an experimented team for at least six months before enlisting.

It is especially important to document:

- the number of severe hypoglycemia episodes, which means requiring another person’s help;
- the frequency of hospitalizations for ketoacidosis;
- the glycaemic lability and the lack of perception of hypoglycemia with assessment of the Hyposcore or lability index;
- the measurement of the lack of perception of hypoglycemia episodes with the Clarke score;
- a 24 hour study of the amplitude of blood glucose excursions especially with an ambulatory continuous monitoring system.

Establishing an indication of islet transplantation is also difficult because transplantation is a point of no return particularly when compared to optimized insulin therapy. Therefore, it is essential to evaluate the candidate’s motivation.

It is necessary to have a good understanding of why the candidate wants an islet transplantation, to inform him about the side effects, the requirement of a work discontinuation for at least three months (the duration of the period of islet infusions with sustained immunosuppression), the necessity of a long-term follow-up taking into account the immunosuppression and the limited duration of insulin independence.

It is often useful to organize a meeting between the candidate and already transplanted patients. The candidate must understand that transplantation is not a magic wand but a relatively difficult procedure, especially during the first three months, even if it is not as demanding as a whole pancreas transplantation.

5. Conclusion

Type 1 diabetes are intrinsically unstable situations due to the loss of insulin secretion along with the loss of glucose sensing.

In diabetes cell therapy, a mean distance of three years on a significant series of patients is now available thanks to the CITR that helps evaluate mid-term results.

These results are not yet equivalent to those of pancreatic transplantation, but associated with fewer side effects. The main factors of success are beginning to be better understood, especially the role of primary graft function, as well as allo- and autoimmunity [28,29]. In contrast, several studies confirm the better efficacy of cell therapy compared to optimized insulin therapy, even in pump, at the cost of more side effects, but with an improvement of some diabetic complications.

Finally, taking into account the respective indications and contra-indications of diabetes cell therapy or the top technologies in brittle diabetes, an islet transplantation could be more specifically proposed to patients presenting a lack of perception of hypoglycemia episodes, extreme lability, dysautonomic neuropathy or in whom optimized insulin therapy has failed.

A technical solution (external pump coupled with a glucose sensor) is an alternative proposed to patients presenting multiple but perceptible hypoglycemic episodes, patients who are overweight or whose daily insulin needs are greater than 1 U/kg per day, with kidney or liver abnormalities or sensitization, making identification of a compatible graft difficult.

The improvement of islet transplantation both in terms of the number of infusions needed and the duration of insulin-independence will help to progressively better define the indications, perhaps thanks to a scoring system that could help give priorities in graft allowance, as has already been done for kidney or liver transplantation.

References


