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

M.-C. Vantyghem\textsuperscript{a,b,*}, F. Defrance\textsuperscript{a}, D. Quintin\textsuperscript{a}, C. Leroy\textsuperscript{a}, V. Raverdi\textsuperscript{c}, G. Prévost\textsuperscript{d}, R. Caiazzo\textsuperscript{c}, J. Kerr-Conte\textsuperscript{b}, F. Glowacki\textsuperscript{e}, M. Hazzan\textsuperscript{b}, C. Noel\textsuperscript{c}, F. Pattou\textsuperscript{b,c}, Diamenord, A.S. Balavoine\textsuperscript{f}, R. Bresson\textsuperscript{g}, M.F. Bourdelle-Hego\textsuperscript{h}, M. Cazaubiel\textsuperscript{f}, M. Cordonnier\textsuperscript{i}, D. Delefosse\textsuperscript{j}, F. Dorey\textsuperscript{j}, A. Fayard\textsuperscript{j}, C. Fermon\textsuperscript{k}, P. Fontaine\textsuperscript{l}, C. Gillot\textsuperscript{g}, S. Haye\textsuperscript{m}, A.C. Le Guillou\textsuperscript{l}, W. Karrouz\textsuperscript{n}, C. Lemaire\textsuperscript{g}, M. Lepeut\textsuperscript{k}, R. Leroy\textsuperscript{m}, B. Mycinski\textsuperscript{o}, E. Parent\textsuperscript{l}, C. Siame\textsuperscript{m}, A. Sterkers\textsuperscript{p}, F. Torres\textsuperscript{p}, O. Verier-Mine\textsuperscript{i}, E. Verlet\textsuperscript{q}, G4 working groups, R. Desailly\textsuperscript{r}, A. Dürrbach\textsuperscript{s}, M. Godin\textsuperscript{t}, J.D. Lalau\textsuperscript{u}, C. Lukas-Croisier\textsuperscript{V}, E. Thervet\textsuperscript{w}, O. Toupance\textsuperscript{x}, Y. Reznik\textsuperscript{y}, P.F. Westeel\textsuperscript{z}

\textsuperscript{a} Endocrinology and Metabolism Department, Inserm U599, Lille University Hospital, C.-Huriez Hospital, 1, rue Polonovski, 59037 Lille cedex, France  
\textsuperscript{b} Diabetes Biotherapy, Inserm U859, Lille University Hospital, Lille, France  
\textsuperscript{c} Endocrine Surgery Department, Lille University Hospital, Lille, France  
\textsuperscript{d} Endocrinology Department, Rouen University Hospital, Rouen, France  
\textsuperscript{e} Nephrology Department, Lille University Hospital, Lille, France  
\textsuperscript{f} Diabetology Department, Tourcoing General Hospital, Tourcoing, France  
\textsuperscript{g} Diabetology Department, Douai General Hospital, Douai, France  
\textsuperscript{h} Diabetology Department, Béthune General Hospital, Béthune, France  
\textsuperscript{i} Diabetology Hospital, Valenciennes General Hospital, Valenciennes, France  
\textsuperscript{j} Diabetology Department, Arras General Hospital, Arras, France  
\textsuperscript{k} Diabetology Department, Roubaix General Hospital, Roubaix, France  
\textsuperscript{l} Diabetology Department, Lille University Hospital, Lille, France  
\textsuperscript{m} Clinic of La Loutre, La Loutre, France  
\textsuperscript{n} Endocrinology Department, Lille University Hospital, Lille, France  
\textsuperscript{o} Diabetology Department, Calais General Hospital, Calais, France  
\textsuperscript{p} Endocrine Surgery Department, Lille University Hospital, Lille, France  
\textsuperscript{q} Diabetology Department, Dunkerque General Hospital, Dunkerque, France  
\textsuperscript{r} Endocrinology Department, Amiens University Hospital, Amiens, France  
\textsuperscript{s} UMR 1014 INSERM, Nephrology Unit, Université Paris-Sud-11, University Hospital of Bicêtre, Kremlin-Bicêtre, France  
\textsuperscript{t} Nephrology Unit, Rouen University Hospital, Rouen, France  
\textsuperscript{u} Endocrinology Department, Amiens University Hospital, Amiens, France  
\textsuperscript{v} Endocrine Department, Reims University Hospital, Reims, France  
\textsuperscript{w} INSERM UMR 5775, HYPARC Department, Nephrology Unit, G.-Pompidou European Hospital, University René-Descartes, Paris, France  
\textsuperscript{x} Nephrology Unit, University Hospital Reims, Reims, France  
\textsuperscript{y} Endocrinology Department, Côte-de-Nacre University Hospital, Caen, France  
\textsuperscript{z} Nephrology Department, Amiens University Hospital, Amiens, France

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\* Corresponding author. Endocrinology and Metabolism Department, Inserm U599, Lille University Hospital, C.-Huriez Hospital, 1, rue Polonovski, 59037 Lille cedex, France. Tel.: +33 3 20 44 41 36; fax: +33 3 20 44 69 85.
E-mail address: mc-vantyghem@chru-lille.fr (M.-C. Vantyghem).

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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.

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1. Introduction

The Diabetes Control and Complications Trial (DCCT) demonstrated the close relationship between microangiopathy and HbA1c levels, and provided evidence of the beneficial effects of improving glycaemic control. However, achieving a good HbA1c level is not so simple, as lowering blood sugar carries a risk of hypoglycaemia. Indeed, type 1 diabetes (T1D) 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].


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].
3.1. Clinical trials

The Edmonton protocol was reproduced with varying success, depending on the experience of the site [5]. In Lille, two intraportal allo-IT clinical trials were launched in 2003, one after kidney transplantation (IAK) and the other with IT alone (ITA). These trials were phase-II, single-arm, observational studies (ClinicalTrials.gov NCT00446264 and NCT01123187) [6] that included C-peptide-negative patients who were in either a brittle T1D state (ITA, n = 14) or IAK (n = 14). Immunosuppression was achieved with the Edmonton regimen (induction with dacluzimab combined with tacrolimus [3–6 ng/mL] and sirolimus [12–15 ng/mL for 3 months, and 7–10 ng/mL thereafter]). Patients received two to three sequential infusions of fresh allogeneic islets from cadaveric donors according to ABO compatibility. Infusions were done through radiological percutaneous catheterization of the portal vein. The primary goal was to achieve insulin independence with an HbA1c level <6.5% within a year of the first transplantation. No deaths, portal thrombosis or kidney graft loss were noted. Rates of insulin independence at 1 year were 71% with ITA and 54% with IAK (72% if the HbA1c threshold was set at <7% instead of 6.5%) [6].

3.2. Eligibility and non-eligibility criteria for IT

These above results were obtained from selected patients. With ITA, the risks imposed by immunosuppression were justified by the severity of the brittle diabetes prognosis, as emphasized by Tattersall [7]. In his study, brittle diabetes was associated with:

- lower quality of life scores (46% vs. 7% in stable diabetes);
- more diabetic ketoacidosis, hypoglycaemia, renal failure and pregnancy complications (19% at 10 years);
- a higher risk of mortality (50% at 5 years), especially in cases of autonomic neuropathy.

The definition of brittle diabetes is not mathematical and depends in part on the tools used to assess it, the patients’ perceptions and the adaptations proposed by the diabetologist. It does, however, require that the main causes of lability are ruled out (such as lipodystrophy, malabsorption, adrenal insufficiency, autonomic neuropathy, dental infection and excessive alcohol intakes). The role of psychological factors in the genesis of lability is still debated, although not accepting the idea of having the chronic disease is not, strictly speaking, brittle diabetes and not a good indication for islet cell therapy, given the inherent constraints of transplantation.

After the main causes of brittle diabetes have been rigorously ruled out, insulin therapy should be optimized with a pump if the patient accepts it, and a glucose sensor if medical insurance reimbursement is obtained. Pump treatment is easy to discontinue if it is not tolerable or fails to provide consistent improvement, whereas once the first islet infusion has been initiated, it is much more difficult to stop immunosuppression – for both medical and ethical reasons – as long as C-peptide levels are detectable.

IT may be considered if, despite this optimization, clinical events, glucose lability (grossly quantified by a standard deviation, despite the use of a continuous glucose monitoring system [CGMS], > 2.2 mmol/L [0.4 g/L]) or hypoglycaemia unawareness (confirmed by a Clarke score ≥ 4) persist [8,9]. The main indications for ITA and IAK are presented in Table 1, with the difference that IAK candidates are already receiving immunosuppressant therapy for their kidney graft, which is why brittle diabetes criteria are not required for this indication. Contraindications to IT are summarized in Table 2 and are mostly the result of common-sense efforts to optimize the benefit–risk ratio.

| Table 1 |
|-------------------------------|-------------------------------|
| Indications for islet transplantation alone (ITA) and after kidney transplantation (IAK). |
| **ITA** | **IAK** |
| **Brittle diabetes** | HbA1c > 7% AND contraindications to double kidney/pancreas transplantation |
| Questioning (number of glucagon injections, need for help to recognize or treat hypoglycaemia during the past year) | In reason of severe macroangiopathic complications or age > 45 years (depending on complications) |
| Mean and SD of blood glucose on meter and CGMS (SD > 40 mg/dL) | OR failure of functional kidney graft with double kidney/pancreas transplantation |
| Daily reproducibility: mean amplitude of highest blood glucose excursions (MAGEs) > 60 mg/dL | AND absence of contraindications to progressive steroid weaning (no history of rejection, steady kidney function) |
| Day-to-day blood glucose reproducibility: mean of daily difference (MODD) > 160 mg/dL | |
| **Frequent or non-felt hypoglycaemia** | |
| % of time in hypoglycaemia on CGMS | |
| Frequency and severity of hypoglycaemias: index of hypoglycaemia (LBGI) > 5 | |
| Frequency and perception of hypoglycaemias: HYPO score > 800 | |
| Perception of hypoglycaemia: Clarke score > 4 | |

SD: standard deviation; CGMS: continuous glucose monitoring system; LBGI: low blood glucose index.
Table 2
Contraindications to islet transplantation.

<table>
<thead>
<tr>
<th>Condition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Detectable fasting or postprandial blood C-peptide (&gt; 0.3 ng/mL)</td>
</tr>
<tr>
<td>Addictions (including tobacco)</td>
</tr>
<tr>
<td>HbA1c &gt; 12%</td>
</tr>
<tr>
<td>Body mass index (BMI) &gt; 28 kg/m² (&gt; 30 kg/m² at some centres)</td>
</tr>
<tr>
<td>Insulin need &gt; 1 U/kg/day</td>
</tr>
<tr>
<td>Progressive complications of diabetes</td>
</tr>
<tr>
<td>Untreated coronary artery</td>
</tr>
<tr>
<td>Unstabilized retinopathy</td>
</tr>
<tr>
<td>Renal alterations</td>
</tr>
<tr>
<td>Proteinuria &gt; 300 mg/24 h</td>
</tr>
<tr>
<td>Creatinine level &gt; 16 mg/L</td>
</tr>
<tr>
<td>Creatinine clearance &lt; 60 mL/min</td>
</tr>
<tr>
<td>Patients with increased risk of complications related to immunosuppression</td>
</tr>
<tr>
<td>Untreated hyperlipidaemia (LDL cholesterol &gt; 130 mg/dL)</td>
</tr>
<tr>
<td>Blood pressure &gt; 160/100 mmHg</td>
</tr>
<tr>
<td>Chronic infection, especially by HCV/HBV</td>
</tr>
<tr>
<td>Progressive neoplasia (except basal cell skin cancer or uterine cervical carcinoma in situ)</td>
</tr>
<tr>
<td>Liver changes (threefold increases in liver enzymes, cholestasis, angioma)</td>
</tr>
<tr>
<td>Anti-HLA antibodies &gt; 20% before transplantation</td>
</tr>
<tr>
<td>Patients using systemic steroids</td>
</tr>
<tr>
<td>Young women who wish to become pregnant</td>
</tr>
<tr>
<td>LDL: low-density lipoprotein; HCV/HBV: hepatitis C/B virus.</td>
</tr>
</tbody>
</table>

restore glucose sensing through transplantation of small quantities of beta-cells to limit glucose variability and hypoglycaemia [10], and improve the quality of life. The first approach, which requires more injections with their inherent risks, limits graft dysfunction due to insufficient insulin mass and improves graft duration. However, the long-term IT prognosis depends on the initial graft function as assessed by the beta score, which itself is correlated to the quality of the glucose profile as assessed by prospective CGMS [11]. In our experience, achieving insulin independence should be the primary aim, taking into account that it is also the expectation of most patients, and the not negligible side-effects can only be justified if long-term benefit is obtained.

3.4. Summary

IT has proven its feasibility and reproducibility over time. This means that the next step is assessment of the long-term benefit–risk ratio both in terms of side-effects and the consequences on diabetes complications.

4. Benefit–risk ratio

4.1. IT results

From 1999 onwards, the results of IT have continued to improve, according to the most recent analysis of data from the Collaborative Islet Transplant Registry (CITR). Out of >600 ITA or IAK recipients with T1D, insulin independence at 3 years post-transplantation increased significantly from 27% in the early days to 44% most recently, while C-peptide levels ≥ 0.3 ng/mL, indicative of islet graft function, have most recently been retained for significantly longer [12]. The 5-year insulin independence rate currently varies from 25% (CITR) to 50% (Lille, using the Edmonton protocol), depending on site expertise and type of immunosuppression. The latter figure is similar to results with whole-pancreas transplantation and has led to medical insurance reimbursement in some countries (Canada, Great Britain and Belgium) [12].

4.2. Comparisons with the best reference techniques

Once the IT technique proved feasible and reproducible in selected patients, the next step was to compare results with the best reference techniques. This was done through a few non-randomized studies of a limited number of subjects.

In a prospective crossover cohort of 45 patients on an ITA waiting list, HbA1c levels were lower at 3 years after transplantation by at least 12,000 IEQ with an immunosuppressive regimen using antilymphocyte serum, tacrolimus and mycophenolate (6.6 ± 0.7%) than in the same patients treated with optimal insulin therapy (7.5 ± 0.9%) [13].

The results of IT (n = 13 patients) were also significantly better in terms of daily insulin needs, HbA1c levels, number of hypoglycaemic episodes and mean glycaemia up to 3 years post-IT compared with patients treated with an intraperitoneal insulin pump (n = 17). However, the number of side-effects/year/patient was four times higher in the IT group than in those treated with a pump [14].

Three years after simultaneous kidney/islet or kidney/whole-pancreas transplantation, HbA1c levels did not differ between the two groups, and kidney function was also identical. Nevertheless, insulin independence was achieved more often with whole-pancreas transplantation (96%) than with IT (31%), albeit at the cost of more adverse events (40% repeat laparotomies) [15]. In other cases, IT results were slightly worse than those of pancreas transplantation (insulin independence: 59% vs. 75%, respectively), but with considerably fewer adverse events [16].

4.3. Side-effects

4.3.1. Related to IT

In the 2011 International Islet Transplant Registry report [12], nearly 50% of patients presented with a side-effect within the first year of transplantation: half of them were potentially life-threatening and related to the infusion; the other half were usually minor and related to immunosuppression (Table 3). Complications of percutaneous intraportal injections under local or general anaesthesia (15% of all serious complications) led to a switch from percutaneous puncture to minisurgery under general anaesthesia at some sites, including Lille; indeed, this injection route has since become routine in Lille and has considerably limited life-threatening complications such as gallbladder puncture and haemorrhage. However, other less-invasive access routes (intramuscular [17], intragastric [18]) are also emerging.
Table 3
Main adverse events reported with islet transplantation.

<table>
<thead>
<tr>
<th>Graft-related</th>
<th>Immunosuppression-related</th>
</tr>
</thead>
<tbody>
<tr>
<td>Portal thrombosis (&lt;2%)</td>
<td>Leukopenia, lymphopenia, anaemia: frequent</td>
</tr>
<tr>
<td>Increased liver enzymes (around 200 IU/L) very</td>
<td>Opportunistic infections: frequent with antilymphocyte</td>
</tr>
<tr>
<td>frequent but transient</td>
<td>immunoglobulins</td>
</tr>
<tr>
<td>Pain</td>
<td>Diarrhoea: depending mainly on preexisting dysautonomia</td>
</tr>
<tr>
<td>Haemorrhage, haematoma: rare with minisurgery</td>
<td>Neoplasms: rare</td>
</tr>
<tr>
<td>Vomiting: not very frequent</td>
<td>Skin cancers: yearly follow-up recommended</td>
</tr>
<tr>
<td>If percutaneous injection: bleeding risk (15%),</td>
<td>Lymphomas: rare</td>
</tr>
<tr>
<td>gallbladder perforation (4%)</td>
<td></td>
</tr>
<tr>
<td>Transient vitreous haemorrhage related to sudden</td>
<td>Aphtosis, oedema: frequent with mTOR inhibitors</td>
</tr>
<tr>
<td>blood glucose normalization</td>
<td>Ovarian cysts in women: frequent with mTOR inhibitors</td>
</tr>
<tr>
<td></td>
<td>Proteinuria: rare</td>
</tr>
<tr>
<td></td>
<td>Hypertension: 30%</td>
</tr>
<tr>
<td></td>
<td>Dyslipidaemia: 30%</td>
</tr>
<tr>
<td></td>
<td>Renal failure: rare, depending on calcineurin inhibitors</td>
</tr>
<tr>
<td></td>
<td>Hyperimmunization, especially after immunosuppressant</td>
</tr>
<tr>
<td></td>
<td>discontinuation (80%)</td>
</tr>
</tbody>
</table>

Data are from the Collaborative Islet Transplant Registry (CITR) [12]; mTOR: mammalian target of rapamycin.

4.3.2. Related to immunosuppressants

Close monitoring is justified due to the risk of decompensation of a pre-existing condition such as dyslipidaemia or hypertension. In Edmonton as in our own experience, the percentage of patients receiving at least one antihypertensive treatment or statin before transplantation (30–40%) rose for each treatment (to 60–70%) at 2 to 5 years post-transplantation.

Sirolimus use promotes the occurrence of mouth ulcers, which may be prevented by pretransplant dental care and rigorous post-transplant oral hygiene using bicarbonate of soda and vitamin therapy.

The development of ovarian cysts and heavy menstrual flow increases the risk of anaemia after two or three surgical interventions, but can be prevented by continuous use of a progestin such as nomegestrol.

4.4. Effects on diabetic microvascular complications

4.4.1. Renal function

The first studies to assess the risk–benefit ratio of diabetes cell therapy over the medium term (4 years) involved 41 patients and reported a risk of worsening renal function, particularly after ITA. The mean creatinine clearance reduction was $-0.4 \text{ mL/min/month}$ per 1.73 m$^2$, with risk factors including a long duration of disease before transplantation, female gender and a history of retinopathy [19]. However, no difference was seen in a prospective comparison [20] of 21 patients transplanted with islets and T1D patients treated with optimal insulin therapy. The reduction in mean creatinine clearance ($-0.3 \text{ mL/min/month}$ per 1.73 m$^2$) did not differ from that of the general population.

Whole-pancreas transplantation leads to improvement of histological lesions and reduction of proteinuria, while creatinine clearance also tends to decrease.

The risk of renal graft loss or acute rejection after IT was also observed and was probably related to immunonversion occurring too suddenly in some IAK transplantation protocols. However, no study of the long-term consequences of IT on renal function compared with a control group is currently available.

4.4.2. Neuropathy

Two years after IAK, a significant improvement in a composite index of nerve conduction velocity was observed; it remained stable thereafter, with no differences in terms of sensory and compound muscle action potentials. The three parameters remained similar to those of a control group of nine kidney-only transplanted patients [21]. Following ITA, however, another (crossover) study failed to show any significant improvement in nerve conduction velocity compared with intensive medical therapy, although a significant improvement was found in sensory nerve conduction velocity compared with pretransplant values [20]. As for pancreas transplants, unlike the DCCT/Epidemiology of Diabetes Interventions and Complications (EDIC) study, no improvement in cardiac autonomic neuropathy (CAN) has been demonstrated following IT [22].

4.4.3. Retinopathy

Several studies have evaluated the impact of IT on the evolution of retinopathy. Compared with patients undergoing optimal insulin therapy, less worsening of retinopathy was observed along with improvement of retinal vascularization [23]. Also, in our experience, early transient vitreous haemorrhage, which resolves spontaneously and is related to a sudden improvement in blood glucose levels, has been seen despite careful pretransplantation ophthalmological assessment. However, improvement in glucose variability appears to have a special favourable impact on retinal oedema. In addition, in
cases involving a strong immunosuppressive regimen, ocular cytomegalovirus infection can arise, the diagnosis of which requires an experienced ophthalmologist and specific treatment.

4.5. Effects on diabetic macrovascular complications

The few studies focused on the evolution of macroangiopathy after IT were cross-sectional, and compared T1D patients who had persistent islet graft function after kidney transplantation with patients who had islet graft loss, pancreas transplantation, kidney-only transplantation or treatment with optimal insulin therapy. The overall survival and cardiovascular mortality rates were significantly better in those with a functional beta-cell mass than in others for up to 7 years post-transplantation. In addition, the CITR showed stabilization of complications, although this result should be interpreted with caution, as nearly 30% of patients were lost to follow-up [12].

4.5.1. Peripheral atherosclerosis

Carotid intima–media thickness has been shown to improve after ITA compared with pretransplantation levels, and progressed more slowly in IAK patients compared with kidney-only transplanted T1D patients [24]. As the carotid intima–media thickness is considered a marker of cardiovascular risk, this improvement probably lowers the risk of cardiovascular-related death.

4.5.2. Acute cardiovascular events

There are no data available on the evaluation of acute cardiovascular events after IT. In our cohort of 40 patients (including 18 IAK) transplanted between 1997 and 2012, there were three deaths and two acute cardiovascular events, mostly occurring 5 years post-IT in IAK patients who had lost their islet function and/or did not accept regular follow-up care. In another study of 42 kidney-transplanted patients who were particularly prone to myocardial complications, IT significantly improved cardiovascular function, especially ejection fraction, after 3 years. It should be borne in mind that with whole-pancreas-only transplantation, which has a survival rate of 92% at 1 year, the main cause of death is a cardiac event despite a functional pancreas graft. To avoid these complications, a rigorous cardiovascular follow-up is recommended after IT in T1D patients.

4.6. Quality of life (QoL)

Most QoL studies have been concordant and show that IT is associated with long-term improvement in QoL [25]. This was related to the resolution of hypoglycaemic episodes and the fear associated with their life-threatening risks. Diabetic complications associated with the long-term course of the disease and the side-effects due to the graft both have a negative impact on QoL, which becomes even more significant when insulin independence is not achieved or is lost. The degree of patient satisfaction was evaluated in only one study, which found it to be better following ITA than IAK [26]. This can be explained by the fact that kidney transplantation is the cause behind most of the improvement in QoL following discontinuation of dialysis, which has a much higher impact on everyday life than multiple insulin injections in diabetes.

4.7. Summary of results

Metabolic control with IT was better than that obtained with the most sophisticated methods of insulin administration available at the time (multiple injections, and subcutaneous and intraperitoneal insulin pumps). This superiority was due to restoration of glucose sensing, albeit at the cost of a four-fold higher frequency of side-effects. Nowadays, the results are similar to those of pancreas transplantation, with a lower rate of severe complications despite the need for two to three islet injections. IT appears to either stabilize or improve both macro- and microvascular complications of diabetes, but there is still a genuine need for long-term prospective clinical studies to evaluate the impact of IT. However, acute cardiovascular events could be prevented through systematic screening and treatment if necessary, especially after IAK.

5. Prognostic factors

The factors that determine the success of IT are still as yet unknown. At present, the CITR reports that the best IT results are obtained with a greater number of infusions and higher IEQ [4,11], lower pretransplantation HbA1c levels, an isolation lab working together with a transplantation centre, older recipient age and lower insulin needs. The role of immunosuppressive treatment is difficult to assess, even after taking into account the major influence of centre experience. Of the many other factors that contribute to IT success, some are linked to the donor and the isolation technique. Factors suggestive of a poor prognosis include long warm or cold ischemia time, elderly donor age, long stay in an intensive care unit and low donor weight. The quality of the enzymes used to digest the pancreas is also important. Also, some factors are related to recipients, such as insulin sensitivity.

5.1. Primary graft function

Graft quality as assessed by the beta score is a major long-term prognostic factor of IT. A beta score ≥ 3 is sufficient to make hypoglycaemia episodes disappear, but a value ≥ 7 is required to optimize glycaemic control and graft duration [11].

5.2. Hypoxia

Within the first 14 days of transplantation, beta-cells are exposed to hypoxia, which promotes apoptosis and necrosis. Islets of Langerhans are highly vascularized structures that require 5–10% pancreatic vascularization, despite making up only 1–2% of the pancreatic parenchymal mass. Isolation and purification can lead to almost complete destruction of the vascular system, so the transplant has then to recreate neo-vascularization. Neovascularization is seen between days 2 and 14 after transplantation and is promoted by vascular endothelial growth factor (VEGF) expression. Neovascularization is
nonetheless insufficient and ultimately has negative effects on beta-cell survival.

5.3. Immunity

Allo- and autoimmunity are currently investigated through both humoral and cell-mediated immune tests. Immune cell testing includes mixed lymphocytic cultures using peripheral blood mononuclear cells from recipients, donors or third parties, the release of interferon as assessed by enzyme-linked immunosorbent spot (ELISpot) assay, cell proliferation evaluated by fluorescence-activated cell sorting (FACS) analysis for Ki-67, and cytokines quantification [27]. However, this cell-immunity investigation is rather complex and not done routinely. The respective clinical roles of cell-mediated and humoral immunity are still a matter of debate. Assessment of humoral immunity has the advantage of being possible to perform in most labs, with results quickly available to enable therapeutic intervention if necessary. On the other hand, cell-mediated immunity offers interesting insights into the mechanisms of rejection.

5.3.1. Alloimmunity

As seen with all types of organ transplants, humoral alloimmunity is a major prognostic factor, as it can lead to graft rejection and loss of islet function. In the Milanese experience, up to 66% of 59 islet recipients showed increases in donor-specific antibodies (DSA) after transplantation in association with HLA-DR mismatches and pretransplant antibody levels > 15%, which were also associated with poorer graft survival [28]. Nevertheless, the data are not always in complete agreement. The CITR report on 303 ITA patients from 1999 to 2008 found that pretransplantation panel-reactive antibodies (PRA) were not predictive of islet graft failure, but their post-transplantation level (PRA > 20%) was associated with a 3.6-fold greater risk of graft failure.

Using the pre-Edmonton immunosuppressant regimen, cellular alloreactivity had no significant effects on IT outcome after 1 year, whereas it proved harmful with a sirolimus-associated regimen [29]. The difference in these results most likely depends on whether highly presensitized patients were excluded, the selection of compatible donors for those with low pretransplant levels of sensitization, the type of immunosuppressive regimen and the quality of graft.

5.3.2. Autoimmunity

As T1D is an autoimmune disease, it makes any attempts at pancreatic or cell transplantation difficult. The best-known humoral immune markers are islet cell antibodies (ICA) and antibodies directed against glutamic acid decarboxylase (GAD), tyrosine phosphatase-related islet antigen 2 (IA2) and, more recently, zinc transporter 8 (ZnT-8). These antibodies, especially when combined at high doses, constitute risk markers for T1D, and are detectable prior to onset and at the beginning of the disease. The long-term detrimental effects of humoral islet autoimmunity were first reported in pancreas transplantation, which showed that the presence of GAD and/or IA2 before transplantation, as well as their post-transplantation increase, were associated with shortened graft survival time [30].

With IT using a pre-Edmonton immunosuppressive protocol, there may be persistence or the onset of humoral autoimmunity to islet antigens. The prognosis worsens with early post-transplantation autoantibody increases regardless of transplant type (ITA or IAK) [2]. However, with IT using the Edmonton protocol, the role of humoral autoimmunity, as assessed after 1 year or before the last transplantation, remains a subject of debate [2,3]. The most recent study showed that recipients with increases in post-transplantation antibodies (especially ZnT-8) had similar initial performances, but significantly lower graft survival, compared with patients without such increases. Induction with antithymocyte globulin was also associated with post-transplantation antibody increases, whereas rapamycin was protective against such increases [2]. In another study, blood autoantibody levels were found to have no significant effects on IT outcome after 1 year in contrast to cellular islet-specific autoimmunity [28].

Studies looking at the role of cell-mediated immunity in the short-term IT prognosis have shown that only pretransplantation cell autoreactivity with either a pre-Edmonton or Edmonton-type immunosuppressant regimen was negatively correlated with C-peptide levels [28].

Overall, islet graft loss is probably affected by the level of immunity, its timing (pre- or post-transplantation), its mechanisms (humoral or cell-mediated) and type of immunosuppressive regimen. Yet the relative importance of each factor is still not completely understood, and immunosuppressive regimens are also not able to completely control autoimmunity.

5.4. Immunosuppressive regimens

No consensus has yet been obtained on the best immunosuppressant regimen, if any. The Edmonton protocol (maintenance with sirolimus and low-dose tacrolimus) is the historical reference immunosuppressant regimen for IT, although numerous other combinations of immunosuppressants have been evaluated (Table 4). One of the most commonly used, the so-called “NIH (National Institutes of Health) protocol”, associates induction by antilymphocyte immunoglobulins with a prednisolone bolus, and maintenance with high-dose tacrolimus and mycophenolate. This is then combined with interleukin (IL)-2 receptor antibody at the second and third infusions, and with etanercept at each islet infusion.

In contrast to the easy-to-use anti-IL-2 receptor antibodies, the administration of antithymoglobulin requires:

1. deep venous access with all its inherent risks;
2. two-day islet culture, the harmful effects of which are still under debate (success at Edmonton was obtained with fresh, non-cultivated islets, and having an isolation centre associated with the clinical transplantation centre was also a factor of success, according to the CITR);
3. use of a steroid bolus;
Table 4
Main studies focused on islet transplantation alone (ITA) and after kidney transplantation (IAK).

<table>
<thead>
<tr>
<th>Author</th>
<th>n</th>
<th>Imunosuppression</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ITA</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Edmonton [3]</td>
<td>7</td>
<td>Edmonton</td>
<td>80% at 1 yr; 10% at 5 yrs</td>
</tr>
<tr>
<td>Minneapolis [50]</td>
<td>8</td>
<td>Induction: ATG, daclizumab, etanercept, then MMF, sir ± tac</td>
<td>II 100%</td>
</tr>
<tr>
<td>Edmonton [5]</td>
<td>36</td>
<td>Edmonton</td>
<td>5 out of 8 &gt; 1 yr, 1 infusion 7000 IEQ/kg</td>
</tr>
<tr>
<td>GRAGIL [51]</td>
<td>10</td>
<td>Basiliximab, sir, tac</td>
<td>1 yr no insulin + A1c &lt; 6.5%; 44%</td>
</tr>
<tr>
<td>Miami [52]</td>
<td>3Gr1</td>
<td>Gr1: alemtuzumab, sir + tac 3 months, then sir-MMF</td>
<td>1 yr no insulin + A1c &lt; 6.5%; 3 out of 10</td>
</tr>
<tr>
<td>Chicago [53]</td>
<td>16Gr2</td>
<td>vs. Gr2: Edmonton</td>
<td>2 yrs no insulin: 2 out of 3 Gr1, 6 out of 16 Gr2</td>
</tr>
<tr>
<td>Brussels [34]</td>
<td>21</td>
<td>ATG, tac, MMF</td>
<td>A1c; Gr1 5.4 ± 0.15%, Gr2 6.3 ± 0.12%</td>
</tr>
<tr>
<td>Minneapolis [54]</td>
<td>6</td>
<td>Induction: ATG, etanercept</td>
<td>No insulin 100%. A1c, Gr1: pre 6.5 ± 0.6%, post</td>
</tr>
<tr>
<td>Lille [6]</td>
<td>14</td>
<td>Edmonton</td>
<td>5.6 ± 0.5%, Gr2: pre 7.8 ± 1.1%, post 5.8 ± 0.3%</td>
</tr>
<tr>
<td>CTR [12]</td>
<td>279</td>
<td>Various</td>
<td>No insulin: 13 out of 21</td>
</tr>
<tr>
<td>Sydney [55]</td>
<td></td>
<td>ATG, then tac + MMF, then sir + MMF</td>
<td>Better than Edmonton protocol by arginine test at 1 yr post-transplant</td>
</tr>
<tr>
<td>Philadelphia [31]</td>
<td></td>
<td>ATG + etanercept, islet culture, then low-dose tac &amp; sir</td>
<td></td>
</tr>
<tr>
<td>Atlanta [56]</td>
<td>4</td>
<td>Daclizumab, then tac, then efalizumab + MMF</td>
<td>100% II after 1 islet infusion</td>
</tr>
<tr>
<td>Dallas [57]</td>
<td>8</td>
<td>ATG + anakintra + etanercept, then MMF</td>
<td></td>
</tr>
<tr>
<td><strong>IAK</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lehmann [58]</td>
<td>9</td>
<td>Edmonton</td>
<td>No insulin: 5 out of 6 &gt; 2 transplants</td>
</tr>
<tr>
<td>Gerber [15]</td>
<td>13</td>
<td>Comparison 13 IAK/25 SPK</td>
<td>A1c: pre 8.7 ± 1.9% vs. post 6.2 ± 0.9%</td>
</tr>
<tr>
<td>Tosso [59]</td>
<td>8</td>
<td>Edmonton (switch day of transplant)</td>
<td>2 no function in IAK; A1c id: 6.3 vs. 5.9%; 1 yr no insulin:</td>
</tr>
<tr>
<td>Cure [60]</td>
<td>7</td>
<td>Conversion to sir/tac 6 months post-KT</td>
<td>13 IAK/96% SPK</td>
</tr>
<tr>
<td>GRAGIL [61]</td>
<td>19</td>
<td>Edmonton</td>
<td>1 yr no insulin: 71% (57)</td>
</tr>
<tr>
<td>CTR [12]</td>
<td>46</td>
<td>Various</td>
<td>No insulin 30%, C-p &gt; 0: 86%, A1c decreased by</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>1.95 ± 0.3%</td>
</tr>
</tbody>
</table>

Most of these results are in the Collaborative Islet Transplant Registry (CTR), especially for insulin independence; yr: years; ATG: antithymocyte globulin; MMF: mycophenolate mofetil; sir: sirolimus; tac: tacrolimus; IEQ: islet equivalents; A1c: glycated haemoglobin; Gr1/2: groups 1/2; C-p: C-peptide; II: insulin independence; KT: kidney transplantation; mo: month; SPK: simultaneous pancreas/kidney transplantation.

4 and profound immunosuppression, which promotes opportunistic infections, especially cytomegalovirus resurgence.

Points 3 and 4 also have inherent diabetogenic effects, although such side-effects could be balanced by a more powerful immunosuppressive effect. Indeed, improved results with the Edmonton protocol were found when anti-IL-2 receptor antibodies were replaced by antithymoglobulins. The study was, however, not randomized and not evaluated on a long-term basis [31].

Other recent studies show that antithymoglobulins do not appear to be the best drugs for controlling post-transplantation humoral allo- and autoimmune reactivity [32]. Other T-cell depleting agents such as alemtuzumab (Campath) and anti-CD3 monoclonal antibodies could be used. In the meantime, drugs that act for both induction and maintenance such as efalizumab, belatacept and alefavect, which act as co-stimulator blockers, as well as non-depleting agents such as Treg, are also under investigation.

The choice of immunosuppressive maintenance regimen is of major importance in IT, as the most commonly used drugs have various effects on glucose metabolism and autoimmunity. Calcineurin inhibitors decrease the survival of beta-cells and level of insulin secretion in a dose-dependent way while increasing insulin resistance [33]. The metabolic effects of sirolimus are much debated and vary according to dose and duration, cell and species type, and environmental factors. Some studies have shown negative effects on proliferation, whereas others show increased basal and stimulated insulin, and reduced apoptosis. Sirolimus extends beta-cell mass and lifespan at least in part via inhibition of mammalian target of rapamycin complex 1 (mTORC1) in spite of impaired glucose homeostasis through disruption of mTORC2 signalling [34]. On the other hand, sirolimus inhibits adipogenesis by decreasing adipocyte numbers and size and predisapocyte differentiation, leading to decreases in subcutaneous and visceral fat in murine models of obesity [35]. These effects could modulate insulin sensitivity and innate immunity, while a central effect on food intake has
also been demonstrated. The effects of mycophenolate mofetil and basiliximab appear to be more neutral, although mild detrimental effects on glucose metabolism have not been completely excluded.

The combination of low-dose tacrolimus and sirolimus can prevent autoimmune beta-cell destruction in mice [36]. Sirolimus can also select specific Treg populations, which could have a beneficial effect on islet survival, whereas tacrolimus appears to be the most powerful drug for controlling immune reactivity [29]. However, tacrolimus has also recently been shown to have detrimental effects on islet revascularization [37].

Thus, the choice of immunosuppressive regimen remains a subject of debate, all the more so as the inherent effects of immunosuppressants are difficult to distinguish from the “isolation centre” effect.

5.5. Hyperimmunization

The high risk of sensitization after IT has been demonstrated by the appearance of anti-donor-specific HLA antibodies, which is related to the need for several donors to achieve insulin independence. This manifests primarily when the immunosuppressive regimen is stopped because of graft failure [38] and may be a barrier to further transplants (islet, pancreas or kidney), which should be taken into consideration even if the long-term evolution of these alloantibodies is not well known. In addition to the potential negative effects on future transplants, the presence of >15% type II PRA and DSA has a negative impact on islet survival. Slow, progressive tapering of the immunosuppressive regimen in cases of graft failure could prevent sensitization.

5.6. Non-specific inflammatory responses

Islets cells are highly sensitive to stress related to the whole isolation process such as brain-death resuscitation, pancreas procurement, and isolation and culture procedures. These events drive the expression of inflammatory genes such as the tissue factor (TF) and monocyte chemotactic protein-1 (MCP-1) genes [39]. Contact with allogeneic blood then triggers thrombotic and inflammatory reactions via cytokines within the first 15 min (instant blood-mediated inflammatory reactions [IBMIRs]) and leads to partial loss of islets. Heparin is generally used to avoid thrombotic events and has a beneficial effect on beta-cell function, as does rapamycin through anti-inflammatory activities. Numerous other agents have been studied, including antithrombin, thrombomodulin, tirofiban, anti-tumour necrosis factor (TNF) drugs and withaferin A. Further clinical studies are now necessary to identify the advantages and side-effects of antithrombin therapy.

6. Future perspectives

There are numerous methods currently under investigation for improving the results of IT at all stages of the transplantation process – from the source of beta-cells to maintenance of functional beta-cells after transplantation.

6.1. Alternative beta-cell sources

The development of IT is currently being impeded by limited donor availability. For this reason, an important research track is focused on alternative sources of insulin-producing cells. Xenotransplantation, especially either free or encapsulated pig islets [40], has been a potential source of increasing beta-cell availability since 1994. However, the results are limited because of IBMIRs, the need for intensive immunosuppressive treatment and the risk of transmitting infectious diseases [41].

However, the possibility of differentiating ductal epithelial cells (both embryonic and adult) and both mesenchymal and haematopoietic stem cells into insulin-secreting cells has been demonstrated in vitro, although there have been no clinical applications to date. Transplantation of insulin-secreting cell lines could be of theoretical interest [42], but the lack of control over their proliferative potential remains a problem and eliminates this technique as a true future prospect.

Living-donor IT is justified as it reduces waiting list time. The technique is used mainly in the US, where around 160 living-donor segmental pancreas transplantations have so far been reported. The technique has proved its feasibility and its relatively low donor morbidity with the percelloscopic technique. Despite the small quantity of islets obtained, the absence of warm ischaemia, minimization of cold ischaemia and possibly less-intensive immunosuppressive regimen have proved to be good prognostic factors of graft survival. Nevertheless, only three IT procedures were performed in this series and only one was successful. There is a risk of diabetes in a third of donors, although this might be prevented by avoiding weight gain [43]. In fact, the living-donor procedure has mainly been attempted in countries with a cultural reluctance to donate organs following brain death.

Imaging techniques aimed at in-vivo evaluation of the functional beta-cell mass are under development, including magnetic resonance imaging (MRI) and luminescence or scintigraphy probes that target islets directly or indirectly through immune responses. Glucagon-like peptide (GLP)-1 analogue receptor scintigraphy is the most advanced technique, but even that is still in a developmental stage [44].

Encapsulation of islets has the advantage of providing an immunological separating membrane between donor islets and recipients. This means that recipients would be spared from immunosuppressive therapy. Despite the absence of immunosuppression, transplantation of encapsulated islets has enabled diabetes to be controlled for 6 months in a porcine recipient [45]. Indeed, the development of sheet-embedded islets has improved islet oxygenation, which nevertheless remains a problem in the long-term.

6.2. Alternative transplantation sites

Alternatives to the invasive intraportal technique are also of major interest. Bone marrow is easily accessible, safe and provides good glycaemic control. In addition to allowing insulin venous drainage, gastric transplantation can be implemented by endoscopy, but is associated with secondary fibrosis. Also,
intramuscular grafts have demonstrated good vascularization of islets and a reduction of IBMIRs, which have led to early and sustained (6-month) islet function both in vitro and in vivo (mini-pigs). Such a transplantation site has already been used in humans undergoing autotransplantation after pancreatectomy, the results of which are pending in a prospective trial [17].

6.3. Adjuvant drugs

There are drugs that aim to minimize autoimmune reactions, islet trophicity, non-immune inflammatory responses and all factors that alter islet engraftment. The few human studies focused on non-insulin treatment of islet graft dysfunction have used the GLP-1 analogue exenatide. This agent showed positive effects on the total IEQ and number of infusions needed to achieve insulin independence, and the need for insulin with islet dysfunction. Exenatide improved insulin and C-peptide secretion [46], as did liraglutide, another incretin that has shown beneficial effects on human islet trophicity in vitro together with antiapoptotic action in vitro. Thus, GLP-1 analogues may be used in vitro during the pretransplantation period, but also in vivo in recipients.

Alpha-1 antitrypsin has anti-inflammatory and antioxidative properties that may enhance pancreatic islet transplantation. It also modulates allo- and autoimmunity [47].

Reparixin, a CXCR1/2 inhibitor (anti-IL-8), improves islet engraftment by reducing the intrahepatic influx of polymorphonuclear leukocytes and natural killer T (NKT) cells. Also, IL-1 receptor antagonists (anakinra) and monoclonal IL-6 receptor antibodies (tocilizumab) are two known anti-inflammatory agents successfully used in the treatment of inflammatory states such as rheumatoid arthritis [57]. They significantly reduce markers of inflammation and cell death in islet cultures, and may be useful for pretreatment culture.

Insulin-like growth factor (IGF)-II prevents proinflammatory cytokine-induced apoptosis and significantly improves islet survival after transplantation [48].

6.4. Induction of immune tolerance

Inducing immune tolerance would enable the immunosuppressive regimen and its associated side-effects to be avoided. Anti-CD3 antibodies, when used for a short time at low doses and immediately after transplantation, can induce apoptosis of T cells and, thus, graft tolerance. In addition, the combined use of rapamycin and granulocyte colony-stimulating factor (GCSF) can also induce immune tolerance, and may easily be applied to clinical transplantation. Furthermore, the co-culture and co-transplantation of islets and bone marrow may also have beneficial effects [49].

7. Conclusion

As demonstrated by the CITR, IT has continuously improved since its turning point in 2000, when the report published by the Edmonton team [3] led to the widespread development of the technology worldwide. After a decade of validation, insulin independence rates have reached 50% at 5 years, a success rate similar to that of pancreas transplantation, but with a much less-invasive technique. However, there are still numerous issues to be resolved, including the scarcity of donors and the immune/non-immune loss of islets. Nevertheless, alongside the technological CGM-pump-algorithm approach, IT will undoubtedly become a new standard for treating the huge increase in T1D cases so far observed in the 21st century.

Disclosure of interest

The authors declare that they have no conflicts of interest concerning this article.

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Appendix A. Supplementary data

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References


