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Case Study

Islet Transplantation in Type 1 Diabetes Mellitus with Hypoglycaemia Unawareness

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Key Learning Points

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1. The primary indications for ICT in T1DM are glycaemic lability and hypoglycaemia unawareness.
2. ICT is an effective, minimally invasive treatment for stabilising glycaemic control, correcting hypoglycaemia unawareness and improving quality of life even when exogenous insulin-independence is not fully achieved. However, the majority of patients require two islet transplants.
3. The need for lifelong immunosuppression, in combination with the limited availability of donor pancreases, currently limits the wider application of ICT, particularly in the treatment of children newly diagnosed with T1DM.
4. New technologies, including macro- and micro-encapsulation, xenotransplantation and stem cell-derived beta cells offer hope for the future of beta cell replacement. Yet, until then, a continued focus on optimising donor pancreases, improving the islet isolation procedure, use of novel immunosuppression, and understanding the mechanisms behind graft loss is required.

Case history

Mrs X is a 62-year-old female. She was diagnosed with Type 1 Diabetes Mellitus (T1DM) at the age of 13, which she has managed with exogenous insulin. Since 2011, Mrs X has used continuous glucose monitoring (CGM) to detect periods of hyperglycaemia, to guide top-up insulin injections. At present, her HbA1C is raised at 7.5% and the estimated GFR is 72 ml per min per 1.73m^2. Mrs X has diabetic retinopathy (diagnosed in 2015) and has had two episodes of vitreous haemorrhage, which were treated with vitrectomy.

To manage her T1DM, Mrs X takes long-acting insulin degludec (Tresiba; 14U OD) and fast-acting insulin (NovoRapid; ratio of 1U:6g carbohydrate with a correction ratio of 1U to lower glucose by 3-4mmol/L). Mrs X takes citalopram and amitriptyline for depression, valsartan for hypertension, atorvastatin and maintenance immunosuppression (mycophenylate 500mg BD, tacrolimus 3mg BD). She has no reported drug allergies. She has never smoked and drinks 10 units of alcohol per week. She lives at home alone and works as a schoolteacher.

On examination, Mrs X has a BMI of 24.1. She has an implanted continuous glucose monitor system (Dexcom G6). There is peripheral neuropathy with loss of sensation on the toes bilaterally. On fundoscopy, some cotton wool spots and hard exudates were observed bilaterally, consistent with diabetic retinopathy.

Mrs X first presented in early 2017 with increasing episodes of hypoglycaemia unawareness, in which she lacked the autonomic symptoms and became increasingly dependent on her CGM to alert her of this. An islet cell transplantation (ICT) was recommended. She underwent screening tests (liver scan, chest X-ray, ECG, blood tests and psychological review) which were all normal. Mrs X had her first ICT in September 2017 and commenced mycophenylate and tacrolimus maintenance immunosuppression.

The ICT procedure was well tolerated. Initially, Mrs X's hypoglycaemic episodes had generally resolved. There was clinical improvement in her retinopathy and HbA1C fell to <7.0%. However, at 3-month follow up there was no significant C-peptide response following a mixed meal tolerance test, and she remained insulin-dependent. Graft function continued to decline, with increasing frequency of corrective insulin dosing. CGM revealed increasing diurnal lability in glycaemia. By 6-month follow up, Mrs X was becoming regularly hypoglycaemic in the early mornings and at 9-month follow-up she experienced hypoglycaemia approximately twice daily without any awareness symptoms. Mrs X was listed for a second top-up ICT, which she was performed in May 2019.

A Role for Islet Cell Transplantation for Hypoglycaemia Unawareness?

Hypoglycaemia is a major cause of morbidity and mortality in Type 1 Diabetes Mellitus (T1DM). The autoimmune destruction of pancreatic beta cells requires exogenous insulin to maintain glycaemic control. Whilst insulin therapy reduces progression of secondary complications, its dose is not physiologically regulated and therefore predisposes to hypoglycaemia. Furthermore,

40% of T1DM patients[1] experience a phenomenon called hypoglycaemia unawareness (HU), in which they lack autonomic warning signs and the ability to manage their hypoglycaemia through a behavioural change such as ingesting glucose. Consequently, HU raises the risk of life-threatening hypoglycaemia by 20-fold in T1DM[2]. HU is a considerable fear and burden that leads to loss of independence and employment, and is therefore a chief unmet need in the management of T1DM.

Current therapies for T1DM with HU mostly do not address the underlying pathophysiology. The usual physiological response to hypoglycaemia includes a counterregulatory glucagon and adrenaline response to restore normoglycemia. In HU, recurrent exposure to hypoglycaemia episodes is thought to impair the strength of these responses[3]. Current first-line therapies for HU include CGM and insulin pumps with low glucose suspend features. These approaches alert or mitigate the risk of hypoglycaemia, but do not treat it per se, and are not successful in all patients. Ultimately, a biological solution offers the greatest hope of restoring normal physiological regulation.

Islet cell transplantation (ICT) has emerged as a promising therapy for T1DM with HU (Figure 1). Whilst 99% of the pancreas is exocrine, only 1% of its mass has endocrine function (the islets of Langerhans, which include the insulin-producing beta-cells). The first successful ICTs were performed in the 1990s and protocol improvements since have led to improved rates of insulin independence in recipients. In particular, ICT has been shown to improve HU. The minimally invasive nature of the procedure makes ICT safer than any whole organ transplant, making ICT an attractive alternative to whole pancreas transplantation.

Clinical benefit

ICT has been shown to improve HU. Leitao and colleagues in 2008[4] conducted a retrospective analysis on 31 T1DM patients with HU who had received ICT. The authors quantified HU using the Clarke score (an 8-item patient-reported questionnaire, where a score of 4+ suggests HU) pre-transplant and at 2-year follow-up. The study found that whilst 26% of subjects remained insulin-independent, the proportion of patients with HU fell from 87% to 13%. Therefore, the study was the first to show that whilst graft function declines following ICT and cannot effectively manage hyperglycaemia alone, minimal graft function is sufficient to abrogate HU in the majority of recipients.

This surprising result has been verified by a later study by Pattou and colleagues (2012)[5], which correlated ICT graft function with glycaemic outcomes. The authors used the beta-score – a composite score of beta cell function out of eight, with two points awarded each for: fasting glucose, HbA1C, stimulated C-peptide and absence of insulin or hypoglycemic agent use. Whilst excellent graft function (7+) was associated with insulin independence in a minority of patients, a beta-score of 3+ was sufficient to predict absence of hypoglycaemic episodes. Despite the shortcomings of ICT in managing chronic hyperglycaemia, the reduction in life-threatening hypoglycaemia establishes a key niche for ICT in the management of T1DM with HU.

More recent studies have validated these initial studies with larger and more robust study designs. In contrast to previous retrospective analyses, The Clinical Islet Transplantation (CIT) Consortium reported a large phase 3 prospective study (CIT-07) to evaluate ICT in 48 T1DM patients with HU in 2016[6]. As per the inclusion criteria, all subjects reported a severe hypoglycaemic episode in the year prior to enrolment; however, only 2/45 patients experienced at 1-year follow-up following ICT and all patients had a reduced Clarke score (suggesting improved HU). Furthermore, the study showed that 87.5% of patients achieved HbA1C <7.0% (up from 40% at baseline). Therefore, although less than half of subjects remained insulin independent at follow-up (replicating the results of previous studies), the work shows that ICT can act in conjunction with insulin therapy to achieve target HbA1C control as well as reduce hypoglycaemia.

The CIT-07 study highlights the general limitations of studying the clinical benefits of ICT. Given that many recipients develop graft failure, the clinical benefits of ICT may not last past the short-term follow-up periods. Furthermore, the study was single-arm, so it is difficult to distinguish the absolute benefits of ICT compared to confounding factors such as greater specialist care and follow-up. Converting to a double-arm design poses the ethical dilemma of continuing medical therapy known to be ineffective at controlling life-threatening HU in a control group[6]. Recently, the first double-arm trial (TRIMECO) has been completed, in which T1DM patients with a history of severe hypoglycaemia were randomised to either ICT immediately or 6-month insulin therapy followed by ICT[7]. As the study design enables the insulin group to benefit from ICT after just 6-month, the study offers some balance between the advantages of a double-arm study and the ethical challenges. The TRIMECO study showed that ICT was associated with improved metabolic control (increased median C-peptide and decreased insulin requirements), showing clinical benefit over conventional medical therapy. The short-term follow-up period is insufficient to assess the durability of this response or compare the incidence of hypoglycaemia reliably. Therefore, balancing long-term follow up with ethical challenges remain key barriers to studying ICT efficacy.

How does ICT reduce hypoglycaemia? Rickels

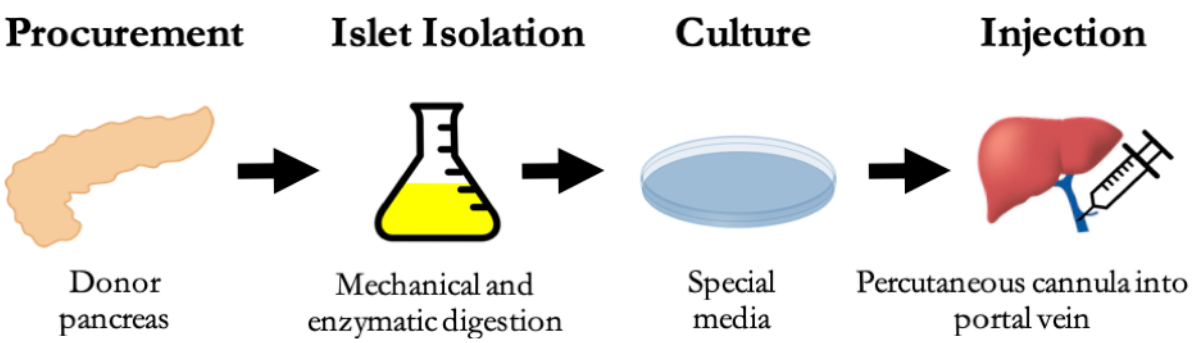

Figure 1: Islet cell transplantation begins with the procurement of pancreas from one (but often multiple decreased donors). Islets are mechanically and enzymatically digested and purified. They are briefly cultured in a specialised media before transplantation by percutaneous injection into the hepatic portal vein. Islet cells then graft into the liver.

and colleagues have investigated hormonal responses after ICT. In their study[8], the authors induced a controlled hypoglycaemic challenge in T1DM control and ICT-recipient patients using a hyperinsulinemic hypoglycaemic clamp. ICT recipients had improved glucagon and adrenaline responses towards those seen in the healthy control population, partially restoring the glucagon counterregulatory response thought to be lost in the pathophysiology of HU. The same authors have used isotope tracing experiments to show that ICT patients reactivate the adrenaline response and upregulate endogenous glucose production under a hypoglycaemic challenge[8]. These studies illustrate that ICT is correlated with reactivating glucagon and adrenaline signalling. In comparison to current first-line therapies for HU (such as insulin pumps with low glucose suspend), which simply mitigate the risk of hypoglycaemia, ICT may reactivate the physiological response that actively treats it.

In contrast to life-threatening acute hypoglycaemia, other studies have assessed whether ICT adequately controls the secondary complications of chronic hyperglycaemia. ICT is associated with improved cardiovascular function and reduced neuropathy. A prospective study by Thompson et. al. (2011)[9] followed microvascular complications after ICT or medical therapy. ICT correlated with improved retinopathy and a smaller decline in glomerular filtration rate (GFR), suggesting increased protection from chronic renal failure. However, this contradicts most other studies, which suggest that ICT is associated with decreased renal function[10] (probably due to nephrotoxic immunosuppression). Furthermore, it is hard to ascribe any benefits of improved glycaemic control specifically to ICT, given that most patients continue to supplement their treatment with insulin. Nevertheless, there is compelling evidence that ICT is associated with some clinical benefit in long-term glycaemic control.

Clinical downfalls

Although ICT is overall relatively safe, the procedure carries minor risks. The most common side effects are bleeding and pain at the site of catheter insertion. Additionally, irritation to the diaphragm causes referred pain to the shoulder tip in half of patients. The main transplantation risk is portal vein thrombosis from percutaneous cannulation. However, heparinisation of the catheter can effectively manage this[11]. The procedure is therefore relatively benign and is still considered safer than any whole organ transplant.

The chief downfall of ICT is the need for lifelong immunosuppression. Induction immunosuppression (typically T-lymphocyte depleting agents such as alemtuzumab) is given to prime the recipient pre-transplant. Following transplant, recipients must take maintenance calcineurin inhibitor-based immunosuppression – typically tacrolimus with mycophenolate. Their long-term use is directly associated with post-transplant lymphoproliferative disorder (PTLD). Furthermore, these agents are directly nephrotoxic - a key disadvantage in the background of chronic renal damage due to diabetes. In the CIT-07 trial, immunosuppression was associated with cytopenias, infection and renal dysfunction[6]. Unsurprisingly, the need for lifelong immunosuppression remains is a key patient concern. It is perhaps the side effect profile of chronic immunosuppression which restricts ICT from adopting a more widespread role in the treatment of T1DM.

Current research is evaluating safer alternative immunosuppressants. Recently, calcineurin-free immunosuppressants – such as efalizumab and belatacept (both inhibiting T-cell activation) have been trialled post-ICT. Efalizumab has been associate with insulin-independence in intrahepatic alloislet recipients, although there are concerns over other unacceptable adverse effects[12]. A current trial (NCT00468403) is evaluating the efficacy and side effect profile of belatacept following ICT, although it has been associated with insulin independence and stable kidney function at 1 year follow up in a smaller study[13]. Whilst these studies may show greater tolerance in the short and medium term, these alternative immunosuppressants are still associated with PTLD. Therefore, it is essential to continue to weigh the risks and benefits of ICT over both the short and long-term time frames.

A key disadvantage of ICT is the frequency of graft failure. Whilst there are patients who remain insulin independent for more than 10 years following ICT, many experience graft failure within a few years[4,6]. Despite the variability – and the associated risks, costs and resources of ICT – there is a lack of prognostic indicators for who will benefit from treatment. Donor and recipients are not currently HLA cross-matched. A fraction of patients develop donor-specific antigens (DSAs)[14], and this is associated with loss of graft function. However, other studies have shown that the presence of DSAs do not reduce graft function, so clearly there are other mechanisms that are relevant. Another limitation is that remaining graft function cannot be quantified after ICT. Current studies are evaluating biomarkers of beta cell death, which will help detect and inform earlier intervention after graft failure.

A large body of ICT research is currently focused on improving graft success. The crudeness of the ICT procedure is believed to damage much of the graft soon after transplant. Upon injection into the portal vein, an instant blood-mediated inflammatory reaction (IBMIR) is believed to lose 50-70% of islets[15]. This process involves an inflammatory reaction including platelet adhesion and leukocyte infiltration. Anti-inflammatory treatment of islets pre-transplantation has shown to improve clinical outcomes. Another source of islet cell loss is hypoxia; revascularisation takes 10-24 days, before which transplanted islets rely on passive diffusion.

This suggests that smaller islets may be more favourable for transplantation survival by improving resilience to hypoxia in this initial phase. Other strategies being investigated are ICT encapsulation or co-transplantation of islets with mesenchymal stem cells, which have both been shown to improve beta cell survival and graft function in preclinical models. Therefore, understanding the source of islet cell damage has room to further optimise the ICT procedure and improve long-term graft function.

Practical considerations

A major practical consideration for ICT is the limited availability of pancreas donors. Even if all cadaveric pancreata were allocated for ICT, based on current organ donor supply, the procedure is estimated to benefit only ~2000 U.S. patients per year. Moreover, there are several inefficiencies and barriers in ICT: the requirement for specialist centres; current isolation techniques yield islets suitable for transplantation in only 60% case[16]; islets from multiple donors are often required to gain sufficient numbers for transplantation. Together with frequent graft failure, there is a strong argument for investing deceased donor pancreas directly for whole pancreas transplantation.

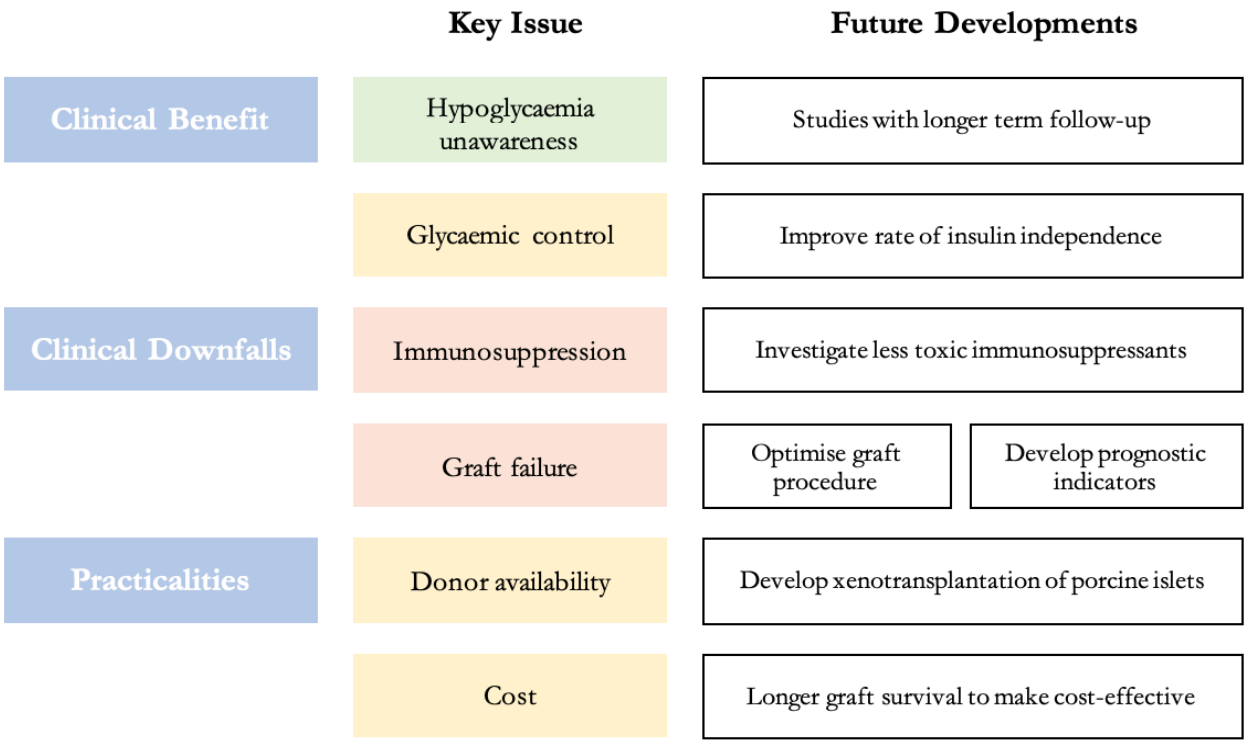

Figure 2: A summary matrix of the key issues surrounding ICT in T1DM with HU. The key advantage of ICT is resolution of hypoglycaemia unawareness (shaded in green). The main drawbacks of ICT are currently the requirement for toxic long-term immunosuppression, and the high rate of graft failure.

In comparison to ICT, the increased risk of major surgery is balanced with a common need for immunosuppression and longer-term graft success. This raises the issue of whether limited cadaveric pancreas should be allocated for ICT in the first place. Xenotransplantation of porcine islets may be a viable alternative source. Proof-of-concept studies have shown reversal of T1DM with ICT of porcine islets into immunosuppressed macaques[17]. More innovation is required to prevent graft rejection without the use of unacceptably toxic immunosuppression. However, the use of porcine islets remains a hypothetical future avenue for now.

The benefit of ICT must be balanced against cost when considering its suitability on a population level. In the TRIMECO trial, the total median cost of ICT at 6-month follow up was over €52,000, compared to just €185 for the insulin group[7]. The main cost is in the islet isolation process, as this requires technical skill and is restricted to specialist centres. However, even the long-term medication cost is more expensive – the cost of immunosuppressants was 28-fold that of insulin medication[7]. A holistic cost analysis would need to consider whether the long-term clinical benefits (such as secondary prevention of future hospital admissions) justify the initial short-term costs of ICT. The results of the STABILOT trial (NCT02854696, expected completion in 2021) should be informative in this respect. If the benefits of ICT can be sustained over a long-term period, the initial costs may be justified – but as it stands, graft failure remains a major barrier to the cost-effectiveness of ICT.

The final practical consideration is how well ICT will stand up to upcoming therapies for T1DM. ICT will need to compete with the rapidly developing technological field. For example, the HypoCOMPaSS trial[18] showed that CGM with insulin pumps could rigorously avoid hypoglycaemia and improve the level at which hypoglycaemia symptoms occurred from 2.6 to 3.1mmol/L. If alternative treatments can improve HU (the main clinical indication for ICT) without issues of donor availability or cost, ICT may not remain a feasible option.

Perspectives

The clinical benefit and risk profile must be tailored to individual patients when deciding who should receive ICT. Evidence suggests ICT confers improved glycaemic control, although the majority of recipients do not stay insulin independent. Given the success of current medical therapies in controlling hyperglycaemia, this is perhaps not a strong enough justification for ICT in the broad population of T1DM. However, most graft recipients experience improved HU; given the acute life-threatening nature of hypoglycaemia, this is perhaps the strongest case in support of ICT in the subset of T1DM complicated with HU.

Given clinical downfalls and practicalities like cost, there needs to be a debate as to how stringent the inclusion criteria should be within the T1DM/HU population. For example, the inclusion criteria for recruitment on the CIT-07 trial was 'failed medical management', but many of these patients had never tried an insulin pump and more than 50% had never used a CGM[6] – all strategies that may have bypassed the need for ICT in the first place if successful. By contrast, the authors of the TRIMECO trial argue for less stringency; in their study, 62% of patients were unable to avoid hypoglycaemia despite being treated with pump therapy and receiving medical and educational management. Again, the stringency of the criteria will further be constrained by the limited donor availability and costs of ICT.

Ultimately, ICT should be targeted to those who will benefit most, but there is currently a lack of prognostic indicators. As the ICT patient population expands and clearer trends of long-term follow-up become available, data should be mined for correlates of good prognosis

and could be used to refine the selection criteria for ICT. This will enable the clinical benefits to last longer, therefore justifying the significant initial resource and cost investments.

Conflicts of interest

None.

Funding

None.

Consent

The patient has consented to the publication of this case study.

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