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Editorial

Pancreatic Islet Transplantation: State of the Art and Future Perspectives

Gianluca Donatini [1, 2, *], Sébastien Giraud [1, 3, 4], Jean-Louis Kraimps [2, 3], Jérôme Danion [1, 2], Thierry Hauet [1, 3, 4, 5, 6]

1. INSERM U1082 (IRTOMIT), Poitiers, F-86000, France; E-Mails: Gianluca.DONATINI@chu-poitiers.fr; giraudseb@yahoo.fr; Jerome.danion@chu-poitiers.fr; thierry.hauet@chu-poitiers.fr
2. CHU de Poitiers, Service de Chirurgie viscérale, Poitiers, F-86000, France; E-Mail: Jean-Louis.KRAIMPS@chu-poitiers.fr
3. Université de Poitiers, Faculté de Médecine et Pharmacie, Poitiers, F-86000, France
4. CHU Poitiers, Service de Biochimie, Poitiers, F-86000, France
5. IBiSA 'plate-forme MOdélisation Préclinique - Innovations Chirurgicale et Technologique (MOPICT), Domaine Expérimental du Magneraud, Surgères, F-17700, France
6. FHU SUPORT 'SUrvival oPtimization in ORgan Transplantation', Poitiers, F-86000, France

* **Correspondence:** Gianluca Donatini; E-Mail: Gianluca.DONATINI@chu-poitiers.fr

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Abstract

Pancreatic islet transplantation represents an effective therapy with lower morbidity for patients carriers of type 1 diabetes compared to whole pancreas transplantation. Although complete insulin independence is usually not achieved it allows control of glycemia balance reducing the risk of severe hypoglycaemia events and impaired awareness of hypoglycaemia. Recent trials had demonstrated islet transplantation to be more effective than current medical treatment and improvements in outcomes also have been reported after the introduction or modification of current immunosuppressive protocols. The principal disadvantage of this technique is the shortage of pancreatic islets/pancreas , needing several donors for 1 recipient, and the inflammation which affected graft viability. These limitations have led researchers to develop alternative way to assure higher effectiveness such as the

development of new cells sources like xenogenic lines (porcine), stem cell-derived β cells or alternative transplantation sites or moreover peculiar techniques to increase cells viability after graft (encapsulation).

Keywords
Pancreatic islet transplantation; diabetes; alterantive β-cell sources

1. Introduction

Human pancreatic islet transplantation (IT) became an effective therapy in selected patients with type 1 diabetes (T1D) [1-4]. Usually this procedure is reserved to those who present unstable T1D with impaired awareness of hypoglycaemia (IAH), severe hypoglycaemic episodes (SHE) and glycemic lability which cannot be controlled by current medical treatment [2-13]. Nevertheless, insulin independence was present after 1 year in less than 10% of all patients treated between 1980 and 1999 [2-5]. Since the introduction of the Edmonton protocol in 2000 it improved to 44% from 2007 to 2010 [5, 14, 15]. According to the last report of the Collaborative Islet Transplant Registry (CITR) to date more than 1.500 procedures have been performed worldwide in 40 recognized centres. Long-term clinical outcomes in selected centres nowadays are comparable to those of whole pancreas transplantation with a 5 years insulin independence rate of 40 to 70% [5]. In patients in which insulin independence is not present at long term, islet transplantation increases anyway outcomes associated with medical therapy, especially regarding SHE [5, 8, 10, 13]. This late was confirmed by the TRIMECO study published in 2018 [12]; the first randomized study on islet transplantation which demonstrated that glycemic control was effective after IT, but also overall glycemic control was easier for those recipients in which graft function was transient [12]. Herein we would like to review the state of the art of pancreatic IT and the new concepts which may modify and ameliorate its outcomes.

2. State of the Art

2.1 Current Indications

Main indication for IT are represented by patients aged >18 years old with a T1D lasting for more than 5 years and who fail to control glycemic balance under appropriate medical monitoring and therapy [1, 5, 6, 9-13]. Glucose metabolic balance of those patients usually is fragile and they present IAH, SHE or labile levels of blood glucose [9]. Other groups of patients which may eligible for IT are patients with T1D after kidney graft and young patients (less than 18 years old) with severe episodes of hypoglycaemia not suitable to other treatments [3, 6]. However, high body-mass-index (BMI) patients (>30 kg/m^2) and patients requiring more than >1.0 U/Kg daily insulin and weighting >90 kg should not be included in IT protocol due to the risk of high insulin resistance [6].

2.2 Islet Isolation

The main limit for IT is represented by the limitations of islets source, indeed islets are isolated from the pancreas of deceased donors [16]. Islet are better isolated in pancreas of donors aged 20 to 50 years, with a BMI>30 kg/m^2 and normal glucose level.

The current isolation technique is nowadays represented by the Automated Method using the Ricordi Chamber which was firstly reported by Ricordi et al. in 1989 and furtherly ameliorated [17]. The theoretical minimal β-cell mass recommended is 5.000 islet equivalent (IEQ) per kg of recipient, but current reports suggest that insulin independence could be better achieved when the IT contains >7.000 IEQ/kg [3, 6]. A normal adult pancreas contains average of 1.000.000 islets, nevertheless, currently 250.000 IEQ per pancreas are obtained after cell isolation [3, 17]. Thus improvement of islet isolation is required. Furthermore, isolation process induced injury that affected islets viability.

2.3 Islet Transplantation

Currently IT is made by transportal infusion [2-4]. The portal vein can be accessed by percutaneous transhepatic approach by an interventional radiologist or by open surgical technique when the first modality is not possible either for anatomical limitations of the liver (angiomas or intrahepatic vascular anomalies) or lack of experienced radiologists [2-4]. Although standardized intraportal IT harbour some risk as post-procedure bleeding, portal thrombosis, mild transaminase elevation, biliary tree lesion [2-4].

3. IBMIR

Instant Blood Mediated Inflammatory Reaction (IBMIR) is a characterized by platelet activation, coagulation and complement system mediated inflammation triggered by the IT when exposed to ABO-compatible blood [18, 19]. It is actually responsible for a substantial loss of islet, measured in between 25% to 50% of the whole islets graft [7, 18, 19]. To prevent IBMIR activated protein C, low molecular weight heparin or islet surface heparinization, have been used with good outcomes [20-22]. TNF-α and IL-1 blockade have been used to reduce the inflammatory response and ameliorate islet's engraftment [23, 24]. Early Natural killer T (NKT) cell mediated action is also responsible of early graft loss and so far trials using molecules which downregulate NKT activation such as α-galactosylceramide or anti-Gr-1-antibody has been made by different groups [25-27]. A better knowledge of all inflammatory mechanisms may ameliorate the islet engraftment reducing the immediate loss of cells due to the IBMIR.

3.1 Immunosuppression

Once the IT has been done the patient undergoes to immunosuppressive therapy by T-cell depletion drugs such as alemtuzumab (anti-CD52 antibody) as in the Edmonton group or thymoglobulin plus etanercept as in the protocol promoted by Hering et al [2-4, 6, 8]. After the induction period a maintenance of immunosuppression has to be performed. The ideal protocol is not still available. So far different drugs help researchers to obtain transplanted islet function. Tacrolimus is an effective inhibitor for allo-rejection but may be responsible of nephrotoxicity,

neurological disorders like tremors and headache and may interfere with insulin secretion [3, 28]. Nevertheless 5-years insulin independence has been achieved in patients on high doses of calcineurin inhibitor, when a sufficient mass of β-cells is transplanted [3, 28].

4. New Concepts

4.1 Islets Isolation and Preservation Improvements

The pancreas preservation, islets isolation and preservation procedures induced injuries, leading the necessity to improvement in order to limit these lesions. Indeed, these delicate procedures impact on the cell integrity, thus have a key role on the low IEQ obtaining, on the islets viability and on pro-inflammatory phenomenon participated to IBMIR injury [29]. It is necessary to improve these procedures pre-IT; advances could be addition of apoptosis inhibitor (to limit the phosphatidylserine expression at cell surface), use of anti-Tissue-Factor or anticoagulant agents, anti-inflammatory drugs or blocking antibodies, which are major actors of IBMIR. The infusion of anticoagulation agents such as dextran sulfate or heparin has been shown to improve islet survival by downregulating the IBMIR response in the experimental setting, but remains to be validated in clinical studies [30]. In addition, after islet isolation, the better time of IT need to be define; freshly versus cultured islets. The islets culture could be an interesting period to control the graft quality and to suppress the necrotic cells prior to IT. However, it seems that the freshly islets have a better viability index compared to cultured [31]. Moreover, graft of freshly human islets to the Nude mice showed better results than graft from cultured islets (24h, 48h, 72h at 37°C) [32].

In order to preserve the graft viability and limit the IBMIR reaction, islets graft encapsulation seems to be a judicious way. Indeed transplantation of pancreatic islets encapsulated within immuno-protective microcapsules is a strategy that has the potential to overcome graft rejection. Nevertheless, one of the major factors limiting the long-term function of encapsulated islets is the pericapsular fibrotic overgrowth [33, 34]. Currently, various strategies to overcome or reduce the pericapsular fibrosis are tested, including alternative capsule materials/composition, co-encapsulation with immunomodulatory cells, administration of pharmacological agents, and alternative transplantation sites.

4.2 Alternative Transplantation Sites

Although the liver is used as the standard site of transplantation it is hampered by the IBMIR reaction, is not suitable for graft removal or biopsy. So far many centres are trying to find an “alternative” site as several report in literature are published. The ideal site should be easily accessible for IT, well vascularized and improves graft survival.

The omentum represents a potentially attractive site because of its rich blood supply with portal drainage, a large surface, easy access for minimally invasive grafting techniques. In a recent report of Baidal et al. a 43-years old patient achieved normal blood glucose levels after omental transplantation [35].

Another site that may avoid IBMIR and is well perfused and oxygenated is represented by the gastric submucosal space. Fujita et al demonstrated feasible in pigs and a trial is ongoing to validate this as an alternative site (trial NCT02402439, University of California, USA) [36].

Finally two specific sites demonstrated to be attractive to researchers: intramuscular and subcutaneous spaces [37-41]. Muscular tissue is characterized by a rich vascular pattern which provides high oxygen flow to islets [37, 38]. Rafael et al. reported a successful auto-transplantation in a 7-years old girl with normal levels of HbA1c throughout 2 years with a C-peptide measured up to 1.37 ng/ml [39]. A pilot study of Bertuzzi et al. validate the site on 4 patients, proving the feasibility, even if engraftment outcome was not effective after 24 months [40].

Subcutaneous IT has been reported by Gala-Lopez et al [41]. By means of a Cell-Pouch®(Sernova Corp, Canada) they inserted pancreatic islet into a plastic mesh-based device with removable plugs in subcutaneous tissue. The graft reversed diabetes in mices but was ineffective in humans [41].

Overall an anatomical site alternative to the liver for IT is still not found, because many parameters should be taken into account. First the degree of vascularization of the site: islet needs a constant blood flow and high tension oxygen to survive after transplantation. Second the eventual traumatism may trigger inflammatory responses that even in the absence of IBMIR could harm the graft. All of these sites are potentially a possible alternative to intraportal IT and further clinical trials are demanded to validate extrahepatic islet transplantation.

4.3 Alternative β-Cell Sources

Due to the limitations of pancreas's donors and the need of using two or three pancreas for a single recipient to achieve a sufficient whole number of IEQ/patient alternative sources of pancreatic islet have been investigated. These include β-cell derived from primary xenotissue and from human stem cell [42-48]. Xenogenic β-cell production has been thought to overcome the demand of human islet: the advantage is an unlimited on-demand supply and absence of ethical issues. Two aspects of xenogenic transplantation should be managed: immune reaction and zoonotic infection transmission. To prevent xenogenic immune reactions multiple immunosuppressive drugs were developed and tested on non-human primates models (NHPM) [49], while although no transmission of porcine viruses has been demonstrated on NHPM, genomic editing technologies may be warranted in the future development of xenogenic-to human IT [50].

Cure of diabetes in small mammals by means of stem cells has been reported recently [45, 46]. To apply to human clinical setting anyway the development of facilities to obtain a large amount of stem cell derived β-cells are needed, as well as a safe and effective transplantation method. To date one multicentric phase I/II trial (NTC02239354, Alberta, Canada) is ongoing. In 2017 ViaCyte further initiated a second trial using a perforated macroencapsulation device containing PEC-01 cells, in which it is anticipated that cell survival will be improved by more optimal neovascularization, but recipients in that trial will require full systemic immunosuppression (PEC-direct™ (VC-02™, NCT03163511).

Researchers implant stem cell at the differentiation phase of endocrine progenitors subcutaneously using a macroencaspulation device to protect cells from allogenic immunity and to reduce the risk of tumour development and given the nature of the graft the protocol do not need any immunosuppression [4].

Indeed the aim of an encapsulation device is to create a protective physical barrier for the transplanted β-cells in order to reduce inflammatory response and avoid the need for

immunosuppression [4, 51]. An ideal device creates a favourable environment which provide rich blood supply to allows normal insulin secretion to maintain normoglycemia and at the same it guarantees adequate cell viability through isolations and protection of the transplant from the immune system and effective nutrient/waste exchange. It should be biocompatible, prevent sensitization and rejection and do not contain potentially tumorigenic cells. Different substances are developed to pursue encapsulation such as alginate coated membranes and hydrogel glucose-permeable devices [52-55]. As peritoneal cavity could provide an adequate environment to implantation of encapsulated islet, a recent trial has been started to assess the effectiveness of alginate membranes (NCT01379729, UZ Brussels, Belgium). Nevertheless, despite the amelioration in biotechnologies for islet encapsulation, translation into clinical investigation has been limited by foreign body inflammatory responses of recipients which is still a limiting factor for its use [4, 51].

5. Conclusions

During the last 30 years IT has become a feasible alternative to whole pancreas transplantation, which harbours a reduced morbidity and, after the introduction of the Edmonton protocol and proper immunosuppressive agents, an equal effectiveness to achieve glycemic control in T1D patients with insulin independence at 5 year of up to 70%. Even in those patients in whom insulin independence is not keep at long-term, recent studies such as the TRIMECO trial favour IT as an effective modality of treatment for T1D if compared with insulin therapy alone [3, 4, 12, 13]. Further researches have to be conducted to ameliorate survival of the transplanted β-cell, as well to find the perfect transplantation site in the human recipient. Xenogenic or stem-cell production of β-cell will moreover allow to satisfy the shortage of islet which limit the use of IT the therapy of choice of T1D.

Author Contributions

Gianluca Donatini: Manuscript draft, Data collection, Manuscript editing, Manuscript revision, Manuscript supervision; Sébastien Giraud: Manuscript draft and revision; Jean-Louis Kraimps: Data collection; Jérôme Danion: Data collection; Thierry Henry: Manuscript supervision.

Competing Interests

The authors have declared that no competing interests exist.

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