

Title Pancreatic islet transplantation

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Aim

The objective of this study was to assess the safety, efficacy and conditions for performance of pancreatic islet (or islets of Langerhans) transplantation (IT) in several indications:

- patients with chronically unstable insulin-dependent diabetes (type 1 diabetes) with preserved renal function (allogeneic transplantation);
- patients with insulin-dependent diabetes and renal failure (usually due to diabetic kidney disease) with an indication for kidney transplantation, in which case IT may be simultaneous or delayed (allogeneic transplantation);
- patients with insulin-dependent diabetes with a functional kidney graft and presenting an HbA1c level $\geq 7\%$ or severe hypoglycaemia (allogeneic transplantation);
- patients at risk of insulinopaenic or insulin-dependent diabetes following extensive or total pancreatic surgery or following a pancreatic injury causing extensive or total devascularisation of the pancreas (autologous transplantation).

This work was also conducted with a view to registration of IT on the list of joint classification of medical procedures (CCAM) and funding by the national health insurance system in France.

Conclusions and results

On the basis of all the available literature (literature with a low level of evidence, clinical practice guidelines in favour of the technique and favourable position of stakeholders), considering the risks associated with severe hypoglycaemia without awareness, the need for these diabetic patients to have better glycaemic control and the particularly unstable nature of diabetes secondary to total pancreatectomy, HAS considers that pancreatic islet (or islets of Langerhans) transplantation (IT) constitutes a treatment option in the following indications:

- patients with chronically unstable insulin-dependent diabetes (type 1 diabetes) with preserved renal function (allogeneic transplantation);
- patients with insulin-dependent diabetes and renal failure (usually due to diabetic kidney disease) with an indication for kidney transplantation, in which case IT may be simultaneous or delayed (allogeneic transplantation);

- patients with insulin-dependent diabetes with a functional kidney graft and presenting an HbA1c level $\geq 7\%$ or severe hypoglycaemia (allogeneic transplantation);
- patients at risk of insulinopaenic or insulin-dependent diabetes following extensive or total pancreatic surgery or following a pancreatic injury causing extensive or total devascularisation of the pancreas (autologous transplantation).

In terms of the role in the care pathway, given all the data and positions collected, HAS considers that:

- allogeneic IT in non-uraemic patients remains a treatment of last resort and is part of the therapeutic arsenal following the failure of optimal diabetes management;
- allogeneic IT is part of the therapeutic arsenal for uraemic patients, and an additional indication for IT is possible: allogeneic islet transplantation following pancreatic graft failure after a double kidney-pancreas transplant;
- autologous IT is reserved for selected cases (children, young patients, non-alcoholic chronic pancreatitis, preserved endocrine function, etc.).

HAS specifies that IT must be performed in accordance with the following recommendations:

- the pancreas must be harvested by a surgeon in accordance with ABM (French Biomedicine Agency) technical guidelines for organ and tissue harvesting, then transported to the islet isolation centre in accordance with the recommendations of the ABM's organ and biological specimen packaging guidelines;
- islet preparation must be performed in accordance with the procedure and using the technical facilities described in the technological assessment report, in a cell therapy unit authorised by the French National Agency for Medicines and Health Products Safety (ANSM) within a healthcare facility and in compliance with applicable regulations;
- the islet isolation team must include at least one engineer and two technicians;
- to achieve an optimal response, the quantity of islets grafted must be more than 10,000 IEQ/kg recipient body weight (from two or even three donors), with a minimum of 200,000 IEQ or 3,500 IEQ/kg recipient body weight at each graft;

- transportation of the islets from the isolation centre to the transplantation centre must be performed in appropriate culture media (transplantation medium (CMRL-1066) supplemented with human albumin (20%) and heparin (35 units/kg recipient body weight) and packaged in approved triple packaging (gas-permeable bag), at 24°C (with continuous temperature control) within a period of 6 to 8 hours;
- selection, preparation, transplantation and follow-up of patients must be carried out by a multidisciplinary team specifically trained in IT, including at least:
 - a diabetes specialist;
 - a transplant specialist (or diabetes specialist trained in the management of immunosuppression);
 - a surgeon and/or interventional radiologist;
 - 24-hour on-call specialist diabetes and transplant teams; an anaesthetist and resuscitation specialist for perioperative management and postoperative monitoring (12-24 hours) in a surgical intermediate care unit;
 - and paramedical personnel (advanced nurse practitioner, operating room nurse, nurse anaesthetist, radiographer, coordinator);
 - a pathologist to quickly confirm that the lesion resected during autologous IT is benign;
- the technical facilities must consist of the following, depending on the surgical approach:
 - a complete interventional radiology room (ultrasonography, angiography room, endoscopy, portal vein pressure measurement) for the transhepatic approach;
 - a visceral surgery operating room for the minimally-invasive laparoscopic approach or a hybrid room;
 - and include 24-hour access to a CT scanner in case of postoperative complications such as haemorrhage;
- depending on the surgical approach, the qualified operator is: either i) a radiologist trained in digestive interventional radiology and experienced in ultrasound-guided portal vein puncture and vascular catheterisation techniques (ideally familiar with portal vein embolisation techniques, which are similar in their approach) but with monitoring of portal pressure; or ii) a trained visceral surgeon specialising in IT.

In addition, HAS highlights the following organisational requirements:

- implementation of mentoring follow-up, with traceability and follow-up of results using the

CUSUM technique put in place by the French Biomedicine Agency (ABM) via the CRISTAL database, which should be made mandatory;

- an agreement with an islet isolation centre approved by the ANSM and capable of handling isolation and transportation of the islets. This centre may be located in the same facility or in another facility;
- for allogeneic transplantation, an agreement with the ABM for inclusion in the national transplant recipient waiting list (CRISTAL), management of organs proposed, follow-up of IT results;
- implementation of a structured organisation and seen with the regional health agencies between hepatic surgeons and urologists on a regional level, supported by an agreement with the ABM.

HAS recommends that the choice of treatment method be based on a joint medical decision shared by the healthcare professionals and the patient. This decision must be founded on the provision of clear, honest information to patients concerning all the available treatment options, taking into account uncertainties relative to efficacy and safety data for IT, particularly in the long term.

Methods

This report was drafted following a rapid assessment method, which consisted of:

- an analysis of the scientific literature:
 - for the allogeneic IT indication, an analysis and an update of the INESSS report published in 2018 (which consists of a systematic review of the literature published between 2000 and 2018) were performed;
 - for the autologous IT indication, a critical analysis of the synthetic literature published before March 2020 (without any study start limit) identified by a systematic search was performed;
- collection of stakeholders' viewpoints, particularly with respect to organisational aspects:
 - professional bodies: French National Council of endocrinology, diabetology and nutrition professionals (CNPEDN), French-language Society for nephrology, dialysis and transplantation (SFNDT), French National Council of visceral and digestive surgery (CNP-CVD), French National Council of anaesthesia and resuscitation and perioperative medicine (CNP-ARMPO), French National Council of transfusion, tissue and cell vigilance and treatment (CNP V3TC), French National Council of radiology and medical imaging (G4);
 - French Biomedicine Agency (ABM);
 - patients' associations: *Fédération française des diabétiques* (French

Diabetics Federation), *France rein* (French kidney association).

Further research/reviews required

Moreover, HAS recommends that the efficacy and safety of IT be reassessed in five years' time on the basis of potential therapeutic advances, such as treatment via semi-automatic insulin delivery systems, and as a function of scientific advances in the preparation of pancreatic islets.

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