REVIEW ARTICLE

Allogeneic transplantation of isolated islet cells in clinical practice*

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KEY WORDS

allogeneic transplantation, diabetes mellitus, islet cells

ABSTRACT

The only clinically acceptable radical treatment for patients with insulin-dependent diabetes mellitus is a whole pancreas transplantation, or alternatively an infusion of isolated islet cells into the hepatic portal venous system. Allogeneic transplantation of isolated islet cells is a procedure used only in a highly specific group of recipients, whereas intensive insulin treatment still remains the best therapy to achieve glycemia control in most patients with type 1 diabetes. Two groups of allograft recipients should be taken into consideration when scheduled for islet cell transplantation. The first group comprises allogeneic kidney recipients with a stabilized graft function for >6 months who receive chronic immunosuppression and require transplantation for end-stage renal disease caused by diabetic nephropathy. The second group consists of patients with unsatisfactory glycemic control despite insulin therapy, life-threatening hypoglycemic episodes and a rapid progression of long-term complications. Despite increasingly beneficial outcomes, islet cell transplantation has several limitations. Maintaining normoglycemia without exogenous insulin administration and appropriate selection of immunosuppressive agents to prolong graft survival are the major challenges. The aim of related studies has been to optimize all phases of islet cell transplantation in order to achieve total insulin independence and prolong graft survival.

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INTRODUCTION Type 1 diabetes (T1D) represents a considerable burden to economy and society associated both with the treatment of the disease and its complications. Currently, the method of choice for maintaining normoglycemia in patients with T1D is an intensive insulin therapy which, if consistently employed, can help prevent long-term diabetic complications and reduce costs of treatment.[1-4] The introduction of insulin pumps into clinical practice has raised the possibility of mimicking the basic, endogenous insulin secretion pattern, which directly relates to a better glycemic control.[1] Despite appropriate treatment, satisfactory and safe control of blood glucose levels still cannot be achieved in a small percentage of patients. We present the current knowledge on allogeneic, isolated pancreatic islet transplantation as the therapeutic option for patients with T1D.[5-7]

Indications for allotransplantation of isolated islet cells Because of the deficiency in organ procurement from multiorgan deceased donors, the waiting list of recipients increases every year. A donor whose pancreas is intended for islet cell isolation has to meet precise criteria, which directly influence transplantation outcomes. The results are also affected by recipient-related risk factors, graft survival and complications of immunosuppression. Therefore, it is necessary to establish strict criteria for referring T1D patients for allogeneic islet cell transplantation (ITx) and to carry out comprehensive evaluation of each individual recipient. There are no clear guidelines regarding indications for ITx. Similar criteria are used in most reference centers where allogeneic islet cell transplantation is performed.

Patients after kidney transplantation The preferred method of treatment in T1D patients who require renal transplantation for end-stage renal disease is simultaneous kidney-pancreas transplantation (KPTx). Current results indicate that solid organ transplantation in such patients has

a greater potential for achieving insulin independence and a substantially longer graft function when compared to ITx. Islet cell transplantation should be considered in patients after KPTx who reject or lose the transplanted pancreas because of complications (vessel thrombosis, infection) or in patients who undergo kidney-alone transplantation for diabetic nephropathy. There is also the question of patients who do not give consent to simultaneous KPTx despite indications, but agree to undergo kidney transplantation and ITx. In those patients the simultaneous kidney-islet cell transplantation should be considered only when reasonable contraindications to simultaneous KPTx occur.

Patients with "brittle diabetes" The method of choice to improve glycemia control in patients with T1D is insulin therapy. The appropriate use of intensive insulin treatment reduces the risk of long-term diabetic complications but increases the risk of dangerous hypoglycemic episodes. In some patients, despite proper insulin therapy, safe blood glucose level cannot be achieved. Transplantation of isolated pancreatic islets can be considered in patients with T1D lasting for >5 years, who suffered from at least 2 episodes of hypoglycemia requiring medical intervention during the last year, and/or with 2 or more hospital admissions for metabolic ketoacidosis. Additional arguments to support ITx are impaired or no awareness of hypoglycemia and a rapid progression of long-term diabetic complications including diabetic nephropathy with albuminuria >300 mg/day, proliferative retinopathy and symptomatic neuropathy. Because of the risk of perioperative complications and a need to use immunosuppression, each potential recipient should be individually evaluated by a team of physicians including a nephrologist, internist, diabetologist, and general practitioner.

Medical criteria for pancreas donor selection

The donor whose pancreas is intended for islet isolation should meet not only general eligibility criteria for multiorgan procurement but also additional requirements including a history of normal glucose tolerance, age between 20 and 65 years (optimal age, 55 years), and body mass index between 20 and 35 kg/m^2 (optimally 25–30 kg/m^2).[8-10] Given the priority attributed to organ transplantation, a multiorgan donor is initially considered as the pancreas donor for solid organ transplantation. Having excluded that possibility, the option of pancreas harvesting for islet cell isolation is considered. Differences between the ideal pancreas donor for solid organ transplantation and the ideal donor for islet isolation make it possible to conduct parallel kidney-pancreas and/or kidney-islet cell transplantation programs.

Pancreas preservation The organ obtained from the cadaveric donor is preserved in a solution at hypothermia of 4°C. Because of the sensitivity of pancreas and islet cells to the effects of warm ischemia, its duration should be reduced to minimum for the procedure to be effective.[11] Placing the preserved pancreas in stable hypothermia slows down metabolism, and consequently limits its hypoxia-related damage to the islet cells.[12] Preserving the pancreas in simple hypothermia using preservation solutions (e.g. University of Wisconsin solution) attenuate but does not halt the process of islet damage. The quantity and quality of isolated islet cells are fundamental to the success of islet cell transplantation procedure.[13,14] Logistic difficulties do not allow to completely eliminate pancreas preservation period between harvesting and isolation process. Therefore, it is vital to optimize conditions for islet cell preservation. Currently, the most commonly used technique is a two-layer method with perfluorocarbon as an artificial oxygen carrier.[15] Based on our own experience, we agree with scientists' skeptical opinions on the two-layer method, which suggests that they should be verified (unpublished data). The continuous perfusion method represents a new trend in preservation of the pancreas as intended for the whole organ transplantation or islet cell isolation. The method and its beneficial effect on kidney intended for transplantation have been clinically well documented.

Isolation and purification of islet cells The pancreas harvested from a deceased multiorgan donor after removing the surrounding tissues is flushed with an antibiotic solution. The organ is then perfused with proteolytic enzymes through the catheter placed in the pancreatic duct. Sliced pieces of pancreas are subject to the enzymatic/mechanic digestion process. Next, the pancreas is rinsed with the hypothermic solution. The obtained mixture of islet cells and exocrine tissue is centrifuged and then separated using continuous density gradient in a cell separator. The purified islet cells are resuspended in the transplant medium to maintain controlled culture in order to evaluate the function and viability of the islets. The long process of pancreatic islet isolation is an essential component of the whole procedure before ITx. Appropriate number of the islet cells must be obtained in order to transplant >5000 islet equivalent (IEQ)/kg of body weight in the first infusion, which corresponds to the islet volume of 150 μm in diameter. When more than one transplantation is required, the cumulative islet mass in 3 infusions has to exceed 10000 IEQ/kg of body weight. Before transplantation, islet suspension is subject to microbiological assessment, endotoxin level measurement, and evaluation of the viability and ability to restore the insulin secretion function.[13]

Islet cell transplantation site The optimal transplantation site for the pancreatic islets should be characterized by high oxygen partial pressure (the oxygen partial pressure in normally

functioning pancreas is 40 mmHg) and the ability to secrete insulin into the circulation from a location with conditions similar to insulin secretion in a healthy person.[16,17] Depending on the transplantation site, a different IEQ number of isolated pancreatic islets is sufficient to maintain insulin independence.[18-20] The contact of the graft with the blood stream should be reduced to a minimum to prevent islet cell loss associated with the reaction of graft's tissue factors and the elements of complement and hemostatic system (instant blood-mediated inflammatory reaction – IBMIR).[21-23] A good access to the transplantation site allows to perform safe and low invasive islet cell implantation. There is no consensus on the optimal transplantation site for pancreatic islets. Therefore, there are ongoing animal model experiments and clinical trials which examine the possibility of islet cell transplantation under the kidney capsule, into the liver, spleen, omental sac, muscles, pancreas, bone marrow and immunologically privileged sites including the thymus, testis and brain. The difficulties for the studies which investigate islet cell transplantation sites include a lack of multicenter, controlled clinical trials and no direct correlation between the animal experiments and the clinical results.[24]

Islet cell transplantation to the recipient's portal venous system The International Islet Transplant Registry demonstrated that in >90% of cases the islet cells are transplanted into the liver through the portal venous access. Despite substantial clinical experience, low islet mass required to maintain insulin independence, and a relatively low invasive access (minilaparotomy with exposing the branch of superior mesenteric vein or transhepatic cannulation of the portal vein's branch under the roentgenoscopy and/or ultrasonography view), wedging the islet cells into the small branches of portal vein is a suboptimal method for ITx. The technique is considered to be responsible for adverse late outcomes of islet cell transplantation. The main disadvantage of the approach is a rapid loss of pancreatic islet function.[23] The factors that contribute to graft injury are mainly IBMIR and accelerated β-cells degranulation.[25] The procedure of islet cell transplantation into the liver through the portal venous access may be limited by method-related complications including bleeding, thrombosis, injury to the biliary ducts and the risk of developing arteriovenous fistula. Despite these limitations, the procedure is used in reference centers all over the world.

Methods of isolated pancreatic islet transplantation used in a clinical experiment or animal experimental studies **Islet cell transplantation under the kidney capsule** The method has not found clinical application because the human kidney capsule has different properties than the rodent capsule and does not provide the graft with appropriate oxygen conditions. Moreover, the infusion of islet cell suspension into the suitable space is a complicated procedure.[2] The method is well-known in animal experiments, particularly on a rodent model, and used to perform studies on isolated islets after infusing the suspension under the kidney capsule. These studies investigate the islet encapsulation types, the toxicity of immunosuppressive drugs, localization and differentiating rejection from degranulation. The method of ITx under the kidney capsule ensures a long-lasting graft function with low islet mass required to obtain insulin independence.[26]

Islet cell transplantation into the spleen The pancreatic islets can be transplanted into the spleen in 2 ways: through infusion of graft into the splenic parenchyma or by splenic vein ligation and a retrograde wedging of the islets into the small branches of the vein. Although there are theoretical advantages of intrasplenic ITx, studies have shown that a relatively high number of islets is required to obtain insulin independence.[27] In clinical practice the method is associated with a higher risk of bleeding or thrombotic complications than the infusion of islet cell suspension into the portal venous system.

Islet cell transplantation into the pancreas The available data on animal models show that the pancreas is an attractive site for the graft transplantation and provides a long-lasting insulin independence with a relatively low islet mass required.[28] The disadvantage of the method is the invasiveness of transplantation procedure and a risk of rapid destruction of grafted cells associated with immunological responses underlying the occurrence of T1D. The results of the method hold promise, however further experimental and clinical studies are needed.

Islet cell transplantation under the gastrointestinal tract mucosa The transplantation of pancreatic islets under the gastric and/or intestinal mucosa has become an interesting and extensively explored direction of the development. The promising results of animal experiments and the possibility of ITx using low invasive endoscopic procedures indicate that the gastrointestinal tract mucosa might be an optimal site for ITx.[29-31] To implement the technique into clinical practice, ongoing animal studies should be completed.

Islet cell transplantation into the immunologically privileged sites The potential advantage of islet cell transplantation into the immunologically privileged sites (the testis, thymus, and brain) is a protective effect of those organs which inhibits or prevents graft rejection. Consequently, it would be possible to maintain the normal graft function with the use of low doses or without the use of immunosuppressive drugs. The thymus represents the most extensively studied

organ for the transplantation of isolated pancreatic islets. Implantation of the islet alloantigens into the thymus based on the negative T lymphocyte selection enables to induce tolerance which allows to achieve normoglycemia without the need to use immunosuppressive regimens.[32] Nevertheless, achieving insulin independence requires transplantation of a relatively large number of islets.[33,34]

The mechanisms which modify the body immune response to the allograft differ between cases. Sertoli cells are recognized as morphological components which have the major role in formation of immunologically privileged sites inside the testis. There are ongoing animal studies that investigate islet cell transplantation directly into the testis. Moreover, islet cell transplantation together with Sertoli cells as an immune response modulator are being explored.[35,36] Despite the extremely promising results of animal experiments, the brain is not considered as a site for transplantation of isolated islet cells because of the moral, ethical and technical issues, and particularly because of the high risk of complications associated with infection.[37]

Immunosuppression The introduction of modern and effective immunosuppressive drugs into clinical practice has revived an interest in the procedure of islet cell transplantation into T1D recipients. A specific group comprises T1D patients following previous organ transplantation (the heart, liver, kidney, pancreas) and receive chronic immunosuppressive therapy. The milestone in the field of islet cell transplantation was the protocol proposed by the Edmonton experts panel in 2000 to use glucocorticoid-free immunosuppressive regimens including sirolimus, tacrolimus and daclizumab and to abandon animal products in the process of preparing the islet suspension.[13] The protocol is still most frequently used in the United States of America – in approximately ½ of all allogeneic transplantations of isolated pancreatic islets. At the same time, there are ongoing trials on new immunosuppressive drugs which would be more effective in preventing islet cell rejection and produce fewer side effects than the currently used drugs. The most advanced studies are associated with the use of monoclonal lymphocyte function-associated antigen-1 antibodies (efalizumab). A single clinical trial is conducted at the University of Emory in Atlanta to prove cytoprotective properties of antibodies directed to β-cells in patients with previously diagnosed T1D.[38] At present, there are similar multicenter studies performed in Europe and the United States of America. Their aim is to develop standards for the procedures of donor recruitment, pancreas procurement, hypothermic preservation, islet cell isolation, transplantation site, recipient qualification, immunosuppressive regimens, graft monitoring and outcome evaluation after 5 years of follow-up.

Outcomes of islet cell transplantation The introduction of glucocorticoid-free immunosuppressive regimens and multiple transplantations to one recipient have contributed to a significant improvement in graft survival.[13] Most commonly, the following outcomes are evaluated: the time of sustained normoglycemia without the need for exogenous insulin injection (which is a period of the total islet cell function) and the period of sustained C-peptide secretion (>0.5 ng/ml) by the grafted islet cells. Depending on the indications for ITx, different time of post-engraftment, sustained insulin independence and the time of detectable C-peptide secretion are observed. The best results are achieved in patients in whom islet cells are transplanted after or simultaneously with kidney transplantation. According to the data of Collaborative Islet Transplantation Registry (CITR) in >80% of patients with islet after kidney transplantation the sustained C-peptide secretion >0.5 ng/ml is maintained for 1000 days compared to 60% of patients who undergo islet transplantation alone. Unfortunately, insulin independence remains for a longer period of time only in a small percentage of patients. After 12 months from the transplantation, in patients who achieve insulin independence, the insulin independence remains in only 75% of patients. After 5 years the percentage falls to 13%. Despite the need for a relatively rapid introduction of exogenous insulin in most patients, insulin requirements after ITx are usually lower, which correlates with acute diabetic complications.[5] The need to develop the program for the transplantation of isolated islet cells is justified by the fact that islet cell recipients have an improved glycose metabolism with no risk of hypoglycemic episodes.

Influence of islet cell transplantation on diabetic complications So far, there have been no large, multicenter, completely controlled clinical studies performed to address the issue as to whether isolated islet cell transplantation inhibits progression of long-term diabetic complications. It results mainly from the discrepancies between individual centers in terms of recipient eligibility criteria, islet cell isolation procedure, and immunosuppressive regimens.[2] Only the uniform procedures and multicenter, prospective clinical studies will answer the above question. An important development has been the founding of the CITR, which includes the majority of North American centers specializing in ITx. Available data show inconsistent results regarding the influence of ITx on kidney function. In patients with transplanted kidneys reduction in microalbuminuria and prolonged graft survival were achieved.[39] On the other hand, there is a rationale suggesting that immunosuppressive nephrotoxic effect after islet transplantation outweighs the nephroprotective effect of normoglycemia.[40] Animal studies have shown that ITx can suppress progression of macroangiopathy, which is corroborated by clinical

effects in humans.[41] Moreover, a significant increase in the retinal blood flow velocity and an inhibited progression of diabetic retinopathy have been described.[42,43] In addition, data showing benefits from ITx in terms of the peripheral nervous system have also been presented.[43,44]

Other directions of the development Many years of clinical observation have shown that the most effective method of treatment for patients with T1D is KPTx. The period of sustained insulin independence following the whole pancreas transplantation is much longer when compared to the transplantation of nonvascularized insulin-secreting cells.[2,45] It should be highlighted that solid organ transplantation program and the follow-up are longer when compared to the ITx program. It is also well known that organ transplantation is not considered as the only choice of treatment in patients with T1D because of the complications associated with the procedure. The therapy is accepted in patients with renal insufficiency who are scheduled for KPTx or pancreas after kidney transplantation. There are ongoing, multicenter studies on the transplantation of nonvascularized insulin-secreting cells, which involve not only the transplantation of allogeneic isolated pancreatic islets from the deceased donor but also of xenogeneic islet cells, encapsulated islets, and insulin-secreting cells derived from stem cells differentiation.[4] The barriers for allogeneic transplantation of isolated islet cells and vascularized organs are the high costs of the procedure and the limited availability of the organs. The solution to the problem may be the xenogeneic transplantation of islet cells derived from the porcine pancreas. Preclinical studies on the porcine ITx into non-human primate model have shown that graft survival with the use of conventional immunosuppressive regiment is very short and lasts from 10 to 56 days.[46,47] Further development may occur due to experimental immunosuppressive therapies using anti-CD154 and anti-interleukin-2 receptor antibodies, balatacept and cytotoxic T-lymphocyte associated protein-4 which prolong graft survival >260 days.[48] Expectations are associated with the possibility of transplanting isolated encapsulated porcine islet cells. Creating a barrier that would separate transplanted islet cells from the elements responsible for immunological and nonimmunological mechanisms of graft damage, while keeping permeability to the substances ensuring appropriate graft function, could help achieve insulin independence without pharmacological modification of the immune response, which in turn would reduce the risk of immunosuppression-related complications. In 1996 Sun et al. presented results of transplanting microencapsulated porcine islets into monkeys with a maximum 803 days of graft survival without use of immunosuppression.[49] Unfortunately, these results have not been reproduced so far.[4] At present, reliable sources estimate graft survival time of isolated, encapsulated islet cells without immunosuppression at 6 months.[50] Clinical studies on transplantation of fetal porcine islet cells into human failed and modified islet cells coated in biodegradable fetal membranes, derived from genetically modified pigs and sheep, are currently in the first and second phases of clinical experiments (press report).

Allogeneic ITx is an alternative method to the whole pancreas transplantation in patients with T1D because of its low invasiveness and safety to the recipient. The mean graft survival time and advances in methods of allogeneic isolated islet cell transplantation provide opportunity for the future to develop "the gold standard treatment of insulin-dependent diabetes". The major challenge for the ITx centers is to develop a uniform program for evaluation of treatment outcomes in a large series of patients and to conduct prospective, controlled clinical trials.

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ARTYKUŁ POGLĄDOWY

Allogeniczne przeszczepianie izolowanych wysp trzustkowych w praktyce klinicznej*

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SŁOWA KLUCZOWE

cukrzyca, przeszczep allogeniczny, wyspy trzustkowe

STRESZCZENIE

Jedyną klinicznie zaakceptowaną radykalną metodą leczenia pacjentów z cukrzycą insulinozależną jest przeszczepienie trzustki narządowej lub, alternatywnie, infuzja izolowanych wysp trzustkowych do żył układu wrotnego wątroby. Przeszczepienie allogeniczne izolowanych wysp trzustkowych (*islet cell transplantation* – ITx) jest procedurą zarezerwowaną dla wąskiej grupy biorców, podczas gdy intensywna insulinoterapia nadal pozostaje najlepszą metodą kontrolowania glikemii u większości chorych cierpiących na cukrzycę typu I. Dwie grupy biorców alloprzeszczpu należy rozważać podczas kwalifikacji pacjentów do transplantacji izolowanych wysp trzustkowych. Pierwsza grupa to biorcy nerki allogenicznej ze stabilną czynnością przeszczepu >6 miesięcy i przewlekłą immunosupresją, którzy wymagali transplantacji z powodu schyłkowej niewydolności nerek w przebiegu nefropatii cukrzycowej. Druga grupa to pacjenci, u których kontrola glikemii za pomocą insulinoterapii nie jest satysfakcjonująca z powodu zagrażających życiu stanów hipoglikemii i/lub szybko narastających powikłań odległych. Pomimo coraz lepszych wyników, przeszczepianie izolowanych wysp trzustkowych stanowi metodę, która ma liczne ograniczenia. Podstawowy problem to utrzymanie normoglikemii bez podaży egzogennej insuliny oraz dobór leków immunosupresyjnych w celu wydłużenia przeżycia graftu. Dotychczasowe badania miały na celu optymalizację wszystkich etapów procedury przeszczepienia izolowanych wysp trzustkowych w celu zwiększenia szansy na uzyskanie całkowitej insulinoniezależności oraz maksymalnego wydłużenia przeżycia graftu.

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