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Islet cells transplantation: pros and cons

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Abstract

Islet cells of the pancreas could be transplanted as a β-cell replacement therapy promising to normalize the blood glucose level in patients with unsteady type 1 diabetes mellitus (T1DM). This mini-review focuses on the pros and cons of the islet cells transplantation. The islet cells transplantation is a safe, effective procedure which could sustain long-term glycemic control and normalization of HbA1c, even prevent severe hypoglycemic episodes. Furthermore, it could control the late diabetes-associated complications. CITR reported that after islet cells transplantation 80% of patients achieved insulin independence, and 73% demonstrated profound correction of glycemic control and decreased HbA1c levels. The two main restriction factors limiting the islet cells transplantation are the insufficient supply of pancreases from deceased donors and the chronic immunosuppressive therapy after transplantation. Additionally, there are still risks for surgical and immunological complications. Concerning the risks of adverse effects during immunosuppressive therapy, the overall rate for malignancies was estimated at about 21% and the death rate following islet transplantation was 2.9%. Overall, the islet cells transplantation is attractive option to treat T1DM avoiding the major surgery and other complications, however, the therapy is not yet fully available due to difficulties of processing multiple scarce pancreas donor organs, the differences in skills and equipment among GMP centers, the lack of appropriate reimbursement. The immunosuppressive therapy becomes safer and more reliable, but the serious limitation to the islet transplantation is the currently low supply of human organ donors. This leads to the need for intensive research in other alternatives like stem-cell or xeno-derived cells for therapy in T1DM.

Keywords: Islet cells, Transplantation, Type 1 diabetes mellitus, Immunosuppressants.

INTRODUCTION

Islet cells of the pancreas could be transplanted as a β-cell replacement therapy promising to normalize effectively the blood glucose levels in selected patients with unsteady type 1 diabetes mellitus (T1DM). More than 1500 patients have been treated by islet transplantation in multiple centers worldwide [1]. Up to date, islet cells transplantation from an experimental procedure transforms into a routine clinical procedure with acceptable efficacy, especially for patients with unpredictable and severe hypoglycemia whose sugar blood levels could not be stabilized safely with the current therapeutic modalities (intensive insulin, pumps, etc.). Furthermore, when performed in experienced centers, islet cell transplantation is considered a safer procedure than pancreas organ transplantation [1].

Historically, pancreatic islets were described firstly in 1869, the progress of pancreatic islet transplantation went through the initial islet isolation, then preclinical model systems, to the first successful allogeneic transplantation of pancreatic fragments in patients with T1DM in 1980. In 2016 the first FDA phase III multicenter trial of islet transplantation for patients with severe T1DM was successfully completed [2].

Pros/Advantages of the islet cells transplantation

The most significant success of the islet cells transplantation is the good clinical outcomes which have led to an increased number of procedures performed in the past two decades [3]. The progress has been made in both sustaining long-term glycemic control and normalization of HbA1c. Today, the procedures achieve not only minimal invasiveness, but the privilege to be routinely performed and successful for completely remove the severe hypoglycemic episodes of the patients' lives [4,5]. Thus, by preventing chronic complications of T1DM, the importance of the early application of islet transplantation is increasing. However, one should have in mind the adverse effects and complications of chronic immunosuppression after transplantation, such as infection, cancer development, nephrotoxicity, which can exceed those of

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conservative treatment of diabetes [1] (see Cons).

Nowadays, with the substantial improvement of clinical isolation facilities used, the utilization rates of processed organs for islet transplantation is estimated between 50-89.5%. Culturing the islet cells for 24–72 h additionally brings benefits: improves quality control, provides time for induction of immunosuppressive therapy, increases purification and minimizes apoptosis and cytokine production which could lead to nonspecific inflammation after the transplantation [7]. Nevertheless, all these GMP-consistent procedures reduce the costs associated with the transplantation of the islet cells [1].

It was established that T-cell depletion for induction therapy had a more significant impact on long-term insulin independence than the maintenance immunosuppression [9]. Furthermore, it was demonstrated that the combination of alemtuzumab and etanercept for induction, and then tacrolimus and mycophenolate mofetil led to higher insulin independence rates at 5 years than huge doses of tacrolimus, sirolimus, and anti-IL-2R antibody [9].

According to the short-term and long-term outcomes in patients with T1DM after islet cells transplantation, the Collaborative Islet Transplant Registry (CITR) reported marked improvement in both, where 80% of patients achieved insulin independence, 73% of them exhibited thorough glycemic control and decreased HbA1c levels, presence of C-peptide, lack of severe hypoglycemic events [10]. Although some concerns were raised initially, the report of CITR registry showed in 2014 that insulin independence rates at the 5th year were similar to these of whole-pancreas transplantation alone [11]. In 2015, the phase III multicentre trial of the NIH CIT Consortium demonstrated the safety and effectiveness of the islet transplantation for patients with complicated T1DM [6, 12].

It is well known that the maintenance of blood sugar level within the reference ranges can prevent several end-organ complications of T1DM. Indeed, cellular replacement of pancreas was shown to restore endogenous C-peptide secretion, reduce retinopathy and diabetes-related renal disease, improve nerve conduction, protect coronary arteries and carotid artery, overall leading to increased survival of the patients [13].

Cons/Disadvantages of the islet cells transplantation

The two main restriction factors that limit the use of islet cells transplantation are the insufficient supply of pancreases from deceased donors and the chronic immunosuppressive therapy after transplantation.

However, the physicians often swing between the risk of poorly controlled T1DM with associated complications and the risks of the long-term administered immunosuppression. Since the latter was improved significantly, the indications for islet cells transplantation expanded also to include children, patients with stable T1DM and T2DM who require insulin [1]. Tacrolimus remains one of the most potent inhibitors, although his nephrotoxicity and related islet toxicity. Interestingly, the latter could be overcome by the infusion of a sufficient number of islets [1].

Regarding the surgical aspects of the intrahepatic islet transplantation, the main risks remain bleeding, portal venous thrombosis, and puncturing the gallbladder. However, the complications could be avoided effectively through treatment of the catheter tract by heparinization and obliteration according to the protocols, as well as using of ultrasound [14].

Another drawbacks of the islet transplantation are the pain at the location of inserted intrahepatic catheter or invoked pain at the shoulder tip (which occur in about 50% of patients and could be treated with standard analgesic medications), the transient elevation of alanine and aspartate transaminases (usually normalize without any intervention), the liver microsteatosis (in up to 20% of the transplanted recipients), rarely bacterial contamination of the pancreatic islet preparation after final purification, etc. [15].

To limit the immunological complications, the protocol for T-cell depletion for induction followed by maintenance suppression by tacrolimus is used, along with avoiding the use of multiple donors` islet products where possible and crossreactive for HLA antigens donors. Using T-cell depletion for induction allows about half of the patients to continue being insulin independent at 5 years after pancreatic islet transplantation [9].

Concerning the risks of complications during immunosuppressive therapy, the overall rate for malignancies was estimated about 21% (most of which treatable skin basal or squamous cell carcinoma), whereas the death rate following islet transplantation was 2.9% (resulted mainly from long-standing end-organ complications from T1DM) [10].

Adding TNF inhibitor or an IL-1 receptor antagonist to the therapy (i.e. anti-TNF/anakinra + etanercept) allows the islets to resist the nonspecific inflammatory reaction when trapped in the portal venules after transplantation, avoiding early loss or decline in graft function [17]. Furthermore, anti-TNF drugs administered amid the islet infusion possess a long-term effect still evident at 5 years after transplantation, thus, improving the outcomes of islet transplantation [9]. However, immunosuppression is not required in case of islet autotransplantation after total pancreatectomy in patients with chronic pancreatitis. In this setting, the early and late graft function (achieved insulin independence, partial or minimal function) depends on the mass of the transplanted islets [18].

Overall, the islet cells transplantation is an attractive option to avoid the major surgery and complications. However, the therapy is not yet fully available due to difficulties of processing multiple scarce pancreas donor organs, the differences in skills and equipment among GMP centers, lack of appropriate reimbursement, etc. The immunosuppressive therapy becomes safer and more reliable, but even the demand for islet transplantation to increase dramatically, the current supply of human organ donors will fail to respond to this demand. This inspires the intensive research in different options for cell therapy in T1DM, such as stem-cell or xeno-derived alternatives.

CONCLUSION

Islet transplantation promises to achieve very desirable aspects of T1DM, such as restoring euglycemia, protecting against glycemic lability and preventing hypoglycemia. All these potential benefits outweigh both exogenous insulin administration (which is often unable to achieve these endpoints) and whole-pancreas transplantation (associated with more risks). The long-term clinical outcomes of islet transplantation were confirmed by the NIH funded phase III multicenter trial. The islet transplantation was established as a safe and effective method for treatments of patients with complicated T1DM (hypoglycemia unawareness and serve hypoglycemic events). Furthermore, in selected centers, the results from islet transplantation were similar to those of pancreas transplantation (whole organ) alone, with T1DM patients sustaining insulin independence at a rate of 50–70% at the 5th year. However, validation and risk: benefit consideration should be assessed more in prospective randomized clinical trials, with long-term follow-up comparing the islet transplantation with conventional treatment of T1DM, such as insulin administration and other advanced artificial pancreas technologies.

Conflict of interest

None declared.

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