MEDICAL SCIENCE MONITOR

EDITORIAL

e-ISSN 1643-3750
© Med Sci Monit, 2023; 29: e941918
DOI: 10.12659/MSM.941918

Received: 2023.07.25
Accepted: 2023.07.25
Available online: 2023.07.26
Published: 2023.08.01

Editorial: First Regulatory Approval for Allogeneic Pancreatic Islet Beta Cell Infusion for Adult Patients with Type 1 Diabetes Mellitus

Dinah V. Parums, MD PhD

Science Editor, Medical Science Monitor, International Scientific Information, Inc., Melville, NY, USA

e-mail: dinah.v.parums@isi-science.com

Conflict of interest: None declared

Abstract Type 1 diabetes mellitus affects adults and children, with an increasing number of newly-diagnosed cases each year. Type 1 diabetes involves a primary functional defect in pancreatic islet beta cells, resulting in secondary autoimmunity that results in T-cell-mediated beta cell death. However, pancreatic transplantation is a complex procedure, with complications that include transplant organ failure due to rejection or ischemia-reperfusion injury, safety issues of the duodenal-duodenal anastomosis technique, and the availability of segmental or whole organs. On June 28, 2023, the FDA Center for Biologics Evaluation and Research (CBER) approved Lantidra (donislecel), the first allogeneic (deceased donor) pancreatic islet cell therapy for the treatment of adults with type 1 diabetes who do not achieve target glycated hemoglobin levels because of repeated episodes of severe hypoglycemia, despite current management. This Editorial aims to highlight the increasing global health burden of type 1 diabetes, previous approaches to pancreatic transplant methods and introduces the first regulatory approval for allogeneic pancreatic islet beta cell infusion, a novel approach to transplantation.

Keywords: **Editorial • Cell Transplantation • Pancreas • Insulin Infusion Systems • Diabetes Mellitus, Type 1**

After the initial discovery and use of insulin in the 1930s, Himsworth was one of the first investigators to make the clinical distinction between type 1 and type 2 diabetes mellitus [1]. By the 1970s, clinical observations identified juvenile-onset or type 1 diabetes, maturity-onset diabetes of the young (MODY), and maturity-onset diabetes, now known as type 2 diabetes mellitus [2]. There was early recognition that insulin was produced by the pancreatic beta cells [2]. Improved studies on the maintenance of functional insulin-secreting pancreatic beta cells, combined with an improved understanding of the human genome, resulted in an increased awareness of the phenotypic spectrum of diabetes [2]. However, there is still some controversy regarding whether type 1 diabetes may be due to a primary functional defect in beta cells, resulting in secondary autoimmunity that results in T-cell-mediated beta cell death [2].

A recently published global epidemiology modeling study by Gregory and colleagues identified that in 2021, there were 8·4 million individuals with type 1 diabetes [3]. There were 1·5 million (18%) >20 years, 5·4 million (64%) aged 20-59 years, and 1·6 million (19%) >60 years [3]. In 2021 there were 0·5 million newly-diagnosed cases with a median age of onset of 39 years [3]. These authors predict that by 2040, the global incidence of cases of type 1 diabetes will increase to between 13·5-17·4 million, which is between 60-107% higher than in 2021 [3].

Transplantation to replace solid organs has a 140-year history that began with an endocrine organ, the thyroid gland [4]. In 1883, the Swiss surgeon, Theodor Kocher (1841-1917), performed the first thyroid transplants in patients with hypothyroidism following surgery for goiter [4,5]. In 1909, Kocher became the first surgeon to win the Nobel Prize for Physiology or Medicine for his discoveries on thyroid gland function [5]. The history of solid organ transplantation of the complex organ, the pancreas, which has both endocrine and exocrine functions, has been more challenging [5]. Identifying the association between pancreatic islet beta cell loss and type 1 diabetes has driven developments in pancreas and beta cell transplantation [6].

In 1966, the first pancreatic transplant was performed at the University of Minnesota, Minneapolis, in a patient with type 1 diabetes [6,7]. During the 1970s and 1980s, segmental pancreatic grafts were used combined with methods to divert secretions from the exocrine pancreas [6]. With the development of improved immunosuppressive agents, three main techniques of pancreas transplantation with enteric diversion have been used, including simultaneous pancreas and kidney transplantation (SPK), pancreas after kidney (PAK) transplantation, and pancreas transplantation alone (PTA) [6]. In March 1980, the first report of the International Pancreas Transplantation Registry (IPTR) allowed for the International Pancreas and Islet Transplantation Association (IPITA), the European Study

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Group for simultaneous Pancreas and Kidney Transplantation (EuroSPK), and European Pancreas and Islet Transplantation Association (EPITA) [6]. However, pancreatic transplantation is a complex procedure, with complications that include transplant organ failure due to rejection or ischemia-reperfusion injury, safety issues of the duodenal-duodenal anastomosis technique, and the availability of segmental or whole organs [6,7].

Transplantation of whole pancreatic islets is challenging for many reasons, including the lack of availability of donor islets, rejection, and the effects of immune suppression [8]. However, stem cell therapies, or substitutes for pancreatic beta cells, have shown promise in preclinical models by reconstituting immune tolerance and preserving pancreatic beta cell function [8]. Mesenchymal stem cells (MSCs), bone marrow hematopoietic stem cells (BM-HSCs), and human embryonic stem cells (hESCs) have been used [8].

A new islet stem cell therapy, VX-880, has been developed by Vertex Pharmaceuticals (Boston, MA, USA) in which pancreatic islet beta cells are grown from allogeneic stem cells using proprietary technology [9]. In February 2021, the US Food and Drug Administration (FDA) approved the application for clinical trials to commence for VX-880 in patients with type 1 diabetes (NCT04786262). VX-880 delivers insulin-producing cells by infusion into the hepatic portal vein under immune suppression [9]. A second treatment approach, VX-264, includes the delivery of the same cells, which are encapsulated and require surgical implantation in the body, but do not require immune suppression [9].

On June 28, 2023, the FDA Center for Biologics Evaluation and Research (CBER) approved Lantidra (donislecel) (CellTrans Inc., Chicago, IL, USA), the first allogeneic (deceased donor) pancreatic islet cell therapy for the treatment of adults with type 1 diabetes who do not achieve target glycated hemoglobin levels because of repeated episodes of severe hypoglycemia, despite current management [10]. Lantidra cell therapy is given as a single infusion into the hepatic portal vein, which may be repeated if the initial dose is inadequate [10,11]. FDA approval was based on the results from two safety and effectiveness non-randomized, single-arm studies that included 30 adults with type 1 diabetes who received between one and three infusions (NCT00566813, NCT00679042, and NCT03791567) [10,11]. At one year, 21/30 study participants no longer required insulin, 11/30 study participants did not require insulin for between one and five years, and 10/30 study participants did not require insulin for more than five years [10,11]. Adverse reactions depended on the number of infusions and included fatigue, anemia, nausea, diarrhea, and abdominal pain [10,11]. More serious adverse reactions were associated with the method of islet cell infusion and immunosuppressive treatment [10,11]. Lantidra differs from stem cell therapy, which is a biological therapy. Recent concerns have been raised by transplant surgery organizations requesting that the regulatory framework for Lantidra cadaveric islets be transferred from the FDA to the Organ Procurement and Transplantation Network (OPTN) and the United Network for Organ Sharing (UNOS) [12].

Conclusions

The increasing global burden of type 1 diabetes has driven new approaches to therapy, which now include the possibility of allogeneic pancreatic islet beta cell transplantation. Early clinical trial data is promising, but remaining challenges require improving cell harvesting and preservation and optimizing post-transplant immune suppression regimens.

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