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Zimislecel, a stem cell–derived islet therapy, demonstrates efficacy in people with type 1 diabetes

Advances in diabetes treatment—through the development of newer and improved insulin formulations, continuous glucose monitoring systems, and increasingly sophisticated automated insulin delivery systems—have substantially facilitated better glycemic control with a lower risk of hypoglycemia in patients with type 1 diabetes mellitus. Despite these advances, achieving good glycemic control remains highly demanding and difficult for most patients, who continue to be exposed to hyperglycemic decompensations, episodes of hypoglycemia, and the development of chronic complications.

In individuals without diabetes, the highly specialized **pancreatic islet beta cells** finely regulate insulin secretion, allowing blood glucose levels to be maintained within a narrow range both after food intake and during fasting periods. In type 1 diabetes, these cells are destroyed by autoimmune attack; therefore, restoring the beta-cell population has long been a major therapeutic goal aimed at curing the disease. This can be achieved through **transplantation**, whereby providing the patient with a new population of beta cells restores normoglycemia and allows discontinuation of insulin therapy. Whole-pancreas transplantation and islet transplantation, using insulin-producing islets isolated from donor pancreata, are the 2 approved therapeutic options for diabetes. In recent years, major advances have been made in research on stem cell–derived islet transplantation, which will be reviewed in this article.

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PANCREAS TRANSPLANTATION AND ISLET TRANSPLANTATION

Pancreas transplantation, particularly when performed simultaneously with kidney transplantation, is the treatment that most consistently restores and maintains long-term normoglycemia. However, due to the scarcity of donor organs and the risks associated with initiating and maintaining immunosuppressive therapy to prevent rejection, pancreas transplantation can be offered to only a very small number of patients. Similarly, although mortality has decreased substantially, pancreas transplantation requires major surgery and is often associated with complications, limiting its use to relatively young patients without severe vascular complications. Thus, pancreas transplantation is a well-established treatment with good outcomes but limited applicability. Islet transplantation, by contrast, is a much simpler procedure, as it involves infusion of islets via injection into the portal vein, without the need for abdominal surgery. This results in a much lower risk of severe complications and allows treatment of patients who would not be candidates for pancreas transplantation. Due to its characteristics, islet transplantation can be repeated multiple times in the same patient until the desired benefit is achieved. Outcomes of islet transplantation are not as favorable as those of combined pancreas–kidney transplantation and are more comparable to pancreas transplantation alone. Approximately 80% of patients achieve insulin independence, although over time a decline in islet function is observed. At 5 years, 50% of patients require insulin again, typically at low doses and with excellent glycemic control. Twenty years after the transplant, 10% of patients remain insulin-independent, and 50% retain some transplanted islet function, resulting in easier glucose control with low insulin requirements (1). Several factors limit islet transplantation to an even smaller number of patients than pancreas transplantation. First, isolating islets from donor pancreata is a complex and highly specialized process requiring dedicated facilities, available in only a few centers worldwide. Second, as with pancreas transplantation, donor scarcity and the risks associated with immunosuppressive therapy restrict patient eligibility. Currently, islet transplantation is indicated in adults with type 1 diabetes mellitus who are unable to achieve near-target HbA1c levels due to recurrent severe hypoglycemia despite structured diabetes education and intensive management.

THE BEGINNINGS OF STEM CELL–DERIVED ISLET TRANSPLANTATION: THE ENCAPTRA TRIAL

One approach to addressing the profound imbalance between the number of patients who could benefit from transplantation and the limited availability of donor organs is to generate insulin-producing islets from alternative sources. In this context, laboratory generation of insulin-producing islets derived from **embryonic stem cells** has progressed rapidly in recent years.

The **first clinical trial** using embryonic stem cell–derived cells began in 2014 with the **Encaptra** device, implanted subcutaneously in the lower back of recipients. Encaptra consisted of a **capsule** containing the transplanted cells. The capsule was semipermeable, allowing nutrients to enter and insulin to exit if produced, while preventing immune cells responsible for rejection from entering. As a result, recipients did not require immunosuppressive therapy. An additional purpose of the capsule was to prevent dispersion of the transplanted cells—whose behavior was not fully predictable—and to allow their retrieval if necessary. The transplanted cells were **progenitor cells**, not yet fully differentiated or mature enough to produce insulin, generated from embryonic stem cells. Based on animal studies, it was expected that these progenitors would complete maturation after transplantation and become capable of insulin secretion within months. The trial demonstrated that the device was safe, well tolerated, and protected transplanted cells from immune attack. Some progenitor cells differentiated into insulin-producing cells. However, cell survival was poor—not due to immune rejection, but to a foreign body reaction that encapsulated and isolated the device, preventing nutrient entry. No functional activity of the transplanted cells was detected in any of the 19 patients enrolled.

In 2017, a **modified device** incorporating fenestrations ("windows") to allow vascular ingrowth was tested to improve nutrient and oxygen delivery. This approach required **immunosuppressive therapy**, as vascular access also allowed immune cells to enter »

THE SHORTAGE OF COMPATIBLE DONORS AND THE RISKS ASSOCIATED WITH IMMUNOSUPPRESSIVE THERAPY LIMIT THE NUMBER OF PATIENTS WITH TYPE 1 DIABETES MELLITUS WHO ARE ELIGIBLE FOR ISLET TRANSPLANTATION

THE ENCAPTRA TRIAL USING EMBRYONIC STEM CELL–DERIVED BETA-CELL PRECURSORS REPRESENTED AN INITIAL ADVANCE, BUT INSULIN PRODUCTION WAS INSUFFICIENT

» the capsule. Results showed insulin presence in 63% of retrieved devices at 3 and 12 months, detectable circulating C-peptide in 6 of 17 patients, and glucose-responsive insulin secretion. However, insulin production remained very low—10 to 100 times lower than required for normoglycemia. Moreover, progenitor cells preferentially differentiated into glucagon-producing alpha cells rather than insulin-producing beta cells. While fenestrations improved vascularization and survival, they also allowed infiltration of host cells that may have compromised graft survival. Immunosuppressive therapy resulted in well-known and clinically significant adverse effects. Despite these limitations, the trial represented an important step forward.

THE ZIMISLECEL TRIAL

Following these 2 clinical trials with promising results, but still without any impact on diabetes control, in late 2021 the biotechnology company **Vertex** announced that the first patient with type 1 diabetes transplanted with pancreatic islets derived from embryonic stem cells, within the framework of a new clinical trial **(VX880-FORWARD)**, had been able to discontinue insulin therapy and maintain strictly normal HbA1c levels. In the summer of 2025, the results obtained in the first 14 patients who completed a 1-year follow-up after transplantation were made public (2).

The product transplanted in the **VX880-FORWARD** trial, known as **Zimislecel**, consists of pancreatic islets obtained—similar to the Encaptra trials—from embryonic stem cells; however, in this case, they are fully **differentiated cells**, not progenitors, that can produce insulin from the time of transplantation. The transplantation procedure is similar to that used for adult donor-derived islet transplantation, namely islet infusion into the portal vein with **implantation in the liver**. The islets are not encapsulated, making **immunosuppressive** therapy necessary. To participate in the trial, patients with type 1 diabetes mellitus had to be 18 to 65 years of age, have, at least, a 5-year history of diabetes, exhibit impaired hypoglycemia awareness, and have experienced, at least, 2 episodes of severe hypoglycemia in the year prior to enrollment. The main endpoints of the trial—which is ongoing with a planned duration of 5 years—are to evaluate the safety and efficacy profile of the treatment. Efficacy is assessed based on the elimination of severe hypoglycemic episodes between days 90 and 365 after Zimislecel infusion, along with an HbA1c < 7% or a reduction of at least 1% at > 1 visits. As a secondary efficacy endpoint, achievement of insulin independence at least once between days 180 and 365, along with a postprandial blood C-peptide level ≥ 100 pmol (indicative of endogenous insulin secretion), is evaluated. The published results describe the progression of 14 patients (4 women and 8 men) who completed, at least, a 1-year follow-up after transplantation. The first 2 patients received half the planned dose of Zimislecel, while the remaining 12 received the full dose. The 12 patients' mean age was 43 years, with a mean course of the disease of 23 years. Prior to treatment, mean HbA1c was 7,8%, with time in range of 49,5%. All patients had experienced 2 to 4 severe hypoglycemic episodes the year before. A total of 8 patients were on subcutaneous insulin infusion pumps, and 6 were using hybrid closed-loop systems. Mean daily insulin dose was 41 units. In all patients, blood C-peptide levels were undetectable, indicating complete absence of endogenous insulin production.

Regarding treatment efficacy, insulin production was detected 3 months after transplantation in the 2 patients who received the half dose of Zimislecel, and unexpectedly, 1 of them was able to discontinue insulin therapy while maintaining normal glucose levels. Due to its significance, this result received widespread international media attention in late 2021 and was presented at the 2022 American Diabetes Association (ADA) meeting. The newly published results show that all patients treated with the full dose of Zimislecel achieved the predefined endpoint of elimination of severe hypoglycemia with HbA1c < 7% as early as 4 months after transplantation, and that this effect was maintained at 1 year. Ten of the 12 patients discontinued insulin therapy, and 0 required its reintroduction. In the remaining 2 patients, insulin dose was reduced by 70% and 36%, respectively. As further indicators of normalized glucose control, all patients (including those still receiving insulin) had time in range > 70% at 150 days and 93% at 1 year, with a glucose coefficient of variation of only 20%. Transplanted islet function, assessed by blood C-peptide levels, was detectable in all patients at 3 months »

THE ZIMISLECEL TRIAL HAS ACHIEVED MAINTENANCE OF NORMAL GLUCOSE LEVELS WITHOUT THE NEED FOR INSULIN OR OTHER GLUCOSE-LOWERING THERAPY — ESSENTIALLY WHAT COULD BE CONSIDERED A CURE FOR DIABETES, ALTHOUGH REQUIRING IMMUNOSUPPRESSIVE TREATMENT

and increased at 6 months and 1 year, indicating sustained survival and function without deterioration.

With respect to treatment safety, the most common adverse events were related either to the islet infusion procedure or to immunosuppressive therapy, similar to what has been described with conventional islet transplantation. There were 2 deaths: 1 due to meningitis following sinus surgery complicated by a skull base fracture, possibly facilitated by immunosuppression; and another due to dementia in a patient with pre-existing cognitive impairment, possibly related to a prior severe traumatic brain injury caused by a hypoglycemia-related traffic accident. To date, no safety issues directly related to the transplanted cells themselves have been identified.

The magnitude of the advance described in this study cannot be overstated. In < 4 years, progress has moved from demonstrating—through the Encaptra trials—that transplanted stem cell–derived progenitor cells could secrete insulin at very low, clinically ineffective levels, to achieving and maintaining nor-

» mal glucose values without insulin or other glucose-lowering therapy—essentially what could be considered a functional cure of diabetes, albeit with the requirement for immunosuppressive treatment.

These results must now be confirmed in the remaining study participants, and long-term follow-up will be particularly important. Only with extended observation will it be possible to determine whether transplanted islets can survive long term and continue to provide sufficient insulin secretion to match or surpass the outcomes of adult donor-derived islet transplantation. From a safety standpoint, although investigators consider the transplanted cells to be fully differentiated—with no remaining stem or progenitor cells capable of generating other cell types—it is essential to confirm this conclusively. There remains a theoretical risk that residual undifferentiated cells could give rise to tumors, a concern that only longer-term follow-up in larger patient populations can definitively exclude.

Pending confirmation on the safety and efficacy of Zimislecel, important technical and medical challenges remain before this therapy can be offered to a significant number of patients. From a technical perspective, reproducibility in islet generation and characterization must be clearly established, and large-scale production capacity developed. The derivation of islets from human embryonic cells raises ethical concerns in some countries and population groups. An alternative research avenue involves generating induced **pluripotent stem cells** from adult cells—either from the patient or from donors—which can then be differentiated into pancreatic islets. From a medical standpoint, the need for immunosuppressive therapy remains one of the major barriers to broader application of transplantation in diabetes. **The risks associated with immunosuppression**—particularly infections and malignancy—are well known and, for most patients, outweigh the risks of continuing insulin therapy. Numerous islet encapsulation strategies have been developed to prevent immune-mediated rejection; however, as demonstrated in the initial Encaptra trial, encapsulation limits islet survival and results in short-lived graft function. Vertex initiated a clinical trial using encapsulated stem cell–derived islets similar to those in VX880-FORWARD implanted subcuta- »

» neously, but this trial was discontinued due to lack of efficacy.

HYPOIMMUNE ISLETS: A PROMISING PATHWAY TOWARD TRANSPLANTATION WITHOUT IMMUNOSUPPRESSION

An attractive alternative to encapsulation systems is the genetic modification of islets to prevent both immune rejection and recurrence of autoimmune attack—so-called **"hypoimmune islets"**. In a study published only weeks after the Zimislecel report, Swedish investigators demonstrated survival of hypoimmune human islets at 12 weeks after transplantation in a patient with type 1 diabetes mellitus without immunosuppressive therapy. The same group had previously reported similar findings in mouse and non-human primate models, successfully preventing not only rejection but also the recurrence of autoimmune beta-cell destruction characteristic of type 1 diabetes mellitus. Although follow-up duration was short and the number of transplanted islets insufficient to expect a clinical impact on glucose control, the study opens a new avenue toward reducing or eliminating the need for immunosuppression, which would substantially expand the pool of transplant candidates. The technique used to generate hypoimmune islets from donor-derived islets may also be applicable to stem cell–derived islets, potentially enabling both unlimited islet availability and avoidance of immunosuppression or encapsulation, thereby overcoming the two principal barriers to widespread transplantation in diabetes.

CONCLUSIONS

Taken together, the 2 investigations published this year represent a major advance toward achieving a cure for type 1 diabetes mellitus. D

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