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DONISLECEL (LANTIDRA) FOR BRITTLE TYPE 1 DIABETES MELLITUS - A NARRATIVE REVIEW

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ABSTRACT

Donislecel (Lantidra) is an excellent stem cell therapy currently in use for the management of brittle type 1 diabetes mellitus. We explored the evolving landscape of Type 1 Diabetes treatment, focusing on Donislecel (Lantidra), the first FDA-approved allogeneic cellular therapy. Integrating innovative therapies like Donislecel with existing treatment options can lay the foundation for enhancing the standard of life for individuals with Type 1 Diabetes. We analyzed four databases, namely Pubmed, Science Direct, Researchgate, and Google Scholar by searching the following keywords: ("Type 1 Diabetes Mellitus") AND ("Donislecel[Lantidra]") AND ("Stem cell therapies") OR ("auto-immune diabetes"). All the available open articles in the English language were reviewed and outlined. It addresses the limitations of traditional management strategies and highlights the potential of Donislecel to enhance glycemic control and reduce insulin dependence. The paper emphasizes the critical need for further research to analyze the longstanding tolerability and safety of Donislecel, ensuring its effective integration into diabetes management strategies.

KEYWORDS: Type 1 Diabetes Mellitus (T1DM), Auto-immune diabetes, Donislecel, Lantidra, Stem cell therapies.

INTRODUCTION

Type 1 diabetes is an auto-immune condition stemming from the inability of the beta cells of the pancreas to produce insulin.[1-3] This occurs due to the damage to these cells caused by auto-antibodies generated by the body's immune response.[2,3] Based on a study published in 2021, persons affected by Type 1 Diabetes were about 8.4 million.[4] The initial management of this condition includes the use of injectable insulin along with regular monitoring of blood glucose levels.[1] Many people face challenges with this treatment option in the form of lethal consequences which

include hypoglycemia and diabetic ketoacidosis.[1] The need for an alternative therapeutic option has led to the shift in focal points towards cellular therapy.[1] Donislecel (Latindra) was validated by the FDA to be the first allogeneic cellular therapy in June 2023.[4] It has been efficacious in maintaining the fasting blood glucose and HBA1C levels within the desired range and also there is a reduction in the instances of hypoglycemia.[1] The trials have also shown that the dependence on insulin decreases completely or partially over the years.[4,5] This review aims to highlight the positive impacts of Donislecel in the management of Type 1 diabetes and also analyze its potential in the future treatment landscape of type 1 diabetes.

REVIEW

The dynamic of diabetes mellitus and its changes over time

The Greek word "diabetes," means "to siphon or pass through," and the Latin word "mellitus," means "honey or sweet," are the sources of the phrase diabetes mellitus.[6,7] In 1910, Sir Edward Albert Sharpey-Schafer proposed that diabetes was caused by a lack of certain substances synthesized by the pancreas. Since the cells in the pancreatic islets of Langerhans create it, he gave it the name insulin, which means island.[7] Sir Harold Percival Himsworth presented a study in 1936 that contrasted type 1 and type 2 diabetes.[8] Following the 1930s' first breakthrough and use of insulin, clinical findings during the 1970s distinguished three types of diabetes mellitus: maturity-onset diabetes of the young (MODY), juvenile-onset, or type 1 diabetes and maturity-onset diabetes, or type 2 diabetes mellitus.[9] Rather than having an insulin insufficiency, Sir Himsworth hypothesized that many patients had insulin resistance, one of the factors that leads to type 2 diabetes is insulin resistance.[8] There is an ongoing discussion on whether type 1 diabetes results from an initial functional deficiency in beta cells, which then triggers secondary autoimmunity and T-cell-conciliated beta cell death. This conflict persists despite efforts to preserve functional insulin-secreting pancreatic beta cells.[9]

Patients with diabetes, whether type 1 or type 2, are affected differently depending on factors including age, race, ethnicity, region, and socioeconomic level.[10] In 2021, 8.4 million individuals worldwide were expected to have T1DM, with 50,000 latest cases reported in that year. By 2040, 13.5–17.3 million people worldwide are expected to have type 1 diabetes.[11] Every year, the prevalence of T1DM rises by 0.34%.[12] Approximately 95% of the approximately 30 million Americans who have diabetes are expected to have type 2 diabetes. An additional 86 million people are at an elevated likelihood of obtaining type 2 diabetes because they have prediabetes.[10]

However, it is rational to anticipate that insulin-insensitive people would acquire diabetes earlier; some accelerators influence this process and the accelerator theory is debatable.[13] Blom et al. (1992) and Knerr et al. (2005) demonstrated that in T1DM children of both sexes compared to normoglycemic controls, the association with T1DM appeared to be related to linear growth rather than obesity.[14,15] Originally presented in 2001, the theory contends that persons with varying genetic origins can develop T1DM and T2DM, two conditions associated with insulin resistance.[16,17] Insulin resistance sets off a chain of events that ultimately end in the autoimmune death of β-cells that are hyper functioning due to glucotoxicity.[18] Furthermore, neo-epitope antigen production, β-cell apoptosis acceleration, and a sharp decline in the secretory ability of insulin have all been linked to insulin resistance brought on by excessive adiposity.[11,19,20]

Stem Cell Therapies for Type 1 DM with Drug Discovery and Development

Research on the association between type 1 diabetes and islet beta cell depletion in the pancreas has led to substantial improvements in both pancreatic and beta cell transplant techniques.[21] The first pancreatic transplant was performed in 1966 at the University of Minnesota in Minneapolis on a patient with type 1 diabetes.[4,21,22] The initial report of the IPTR in March 1980 made possible the establishment of the International Pancreas and Islet Transplantation Association (EPITA), the European Study Group for Simultaneous Pancreas and Kidney Transplantation (EuroSPK), and the International Pancreas Transplantation Registry (IPTR).[4,21] The operation of pancreas transplantation is intricate and fraught with potential difficulties, such as organ rejection, ischemia-reperfusion damage, concerns about the duodenal anastomosis technique, and limited accessibility of organs, either whole or in segments, immune suppression, donor islet scarcity, and transplant rejection.[21-24]

Preclinical animals have shown promise in stem cell treatments, such as pancreatic beta cell replacements, which aim to preserve pancreatic beta cell function and restore immunological tolerance.[23]

REFERENCE	THERAPY	PHASE OF CLINICAL TRIAL	AIM	APPROVAL STATUS
Parums et. Al.(4) NCT04786262	VX-880, islet stem cell therapy	PHASE 1/2	a potential stem cell treatment to stabilize blood sugar levels and boost endogenous insulin synthesis in individuals with type 1 diabetes (T1DM)	Approved by FDA for trial (February 2021)
Parums et. Al.(18) NCT04786262	VX-264, islet stem cell therapy	PHASE 1/2	the administration of the same encapsulated cells, which don't need immune suppression, but must be surgically implanted in the body	Approved by FDA for trial (March,2023)
NCT03162926	VC-02, Combination Product	EARLY PHASE 1	The goal is to determine whether or not participants with Type 1 Diabetes may safely have the VC-02TM combination product implanted subcutaneously and maintained for up to four (4) months.	Not Approved by FDA
Shapiro et. Al.(25) NCT03163511	VC-02, Combination Product	Phase 1/2	The goal of this experiment is to determine whether or not individuals with Type 1 Diabetes may safely have the VC-02TM combo product implanted subcutaneously and maintained for up to two years.	Not Approved
Carlsson et. Al. (26) NCT03406585	Allogenic Wharton's jelly-derived mesenchymal stromal cells (MSCs)	Phase 1/2	This research sought to determine if using allogenic Wharton's jelly-derived mesenchymal stromal cells (MSCs) as a therapy for type recent-onset type 1 diabetes would be safe and effective.	Not Approved
Parums et. Al (4) NCT03791567	(donislecel) Lantidra cell therapy	Phase 3	the first pancreatic islet cell treatment from an allogeneic (deceased donor) to treat individuals with type 1 diabetes recurrently experiencing hypoglycemia and are unable to achieve target glycated hemoglobin levels despite using current medication.	Approved by the FDA for the treatment of adults (first stem cell therapy)

DONISLECEL CLINICAL TRIAL AND THEIR REGULATORY APPROVAL

The FDA's Cellular, Tissue, and Gene Therapies Advisory Committee voted with 12 Yes and 4 No on April 15, 2021, to approve the biologics license application (BLA) 125734, which aims to commercialize a cell therapy product called Donislecel—a commercial trade name for Lantidra—made of allogenic islets of Langerhans. The medicine is designed to treat people with type 1 diabetes mellitus (T1D) whose symptoms do not improve even after receiving a high dose of insulin.[27,28] Additionally, the decision aligns with the outcomes of four recently published, successful multicenter phase 3 clinical trials involving islet transplantation: CIT06 (pivotal trial)[27], CIT-07 (multicenter, single-arm)[28], REP0211 (multicenter, double-blind, randomized)[29], TRIMECO (multicenter, open-label, randomized) and REP0211 (multicenter, double-blind, randomized).[29]

Study Number	Study Phase	Title	Outcome
CIT-O7	3	Allogenic Purified Human Pancreatic Islet (PHPI) Transplantation for treatment of Type 1 Diabetes.	In individuals with persistent impaired self-realization of hypoglycemia and extreme hypoglycemic events, transplanted PHPI provided glycemic control, restored awareness of hypoglycemia, and protected against severe hypoglycemic events 71% of individuals after two years, and 87.5% of subjects at one year had effectively met the targeted initial endpoint.
CIT-06	3	Islet Transplantation in Type I Diabetic Kidney Allograft Recipients: Efficacy of Islet After Kidney Transplantation.	A year after transplant, 62.5% of patients attained the main goal of not experiencing extreme hypoglycemia incidents and had an HbA1c of less than 6.5% or decreased by more than one percentage point, indicating the effectiveness of PHPI transplantation.
TRIMECO	3	Islet transplantation versus insulin therapy in patients with type 1 diabetes with severe hypoglycaemia or poory controlled glycemic after kidney transplantation (TRIMECO): a multicenter, randomized controlled trial	12 months following the initial infusion, four (7% [2–18]) out of 55 infusions had experienced bleeding complications. Furthermore, the median glomerular filtration rate fell from 90·5 mL/min (IQR 76·6–94·0) to 71·8 mL/min (59·0-89·0) among islet recipients who had not previously undergone a kidney transplant, and from 63·0 mL/min (55·0-71·0) to 57·0 mL/min (45·5–65·1). Islet transplantation successfully enhances metabolic outcomes for indications evaluated in this study.
REP0211	3	Targeting CXCR1/2 Does Not Improve Insulin Secretion After Pancreatic Islet Transplantation: A Phase 3, Double-Blind, Randomized, Placebo-Controlled Trial in Type 1 Diabetes	Analysis of patient subsets showed that patients receiving reparixin had a greater percentage of subjects who maintained insulin independence for a year after a single islet infusion than patients receiving placebo (26.7% vs. 0%, P = 0.09) when anti-thymocyte globulin was used as induction immunosuppression.

The University of Illinois Hospital and Health Sciences Center (UI Health) started developing Donislecel in 2004.[30] Donislecel was designated as an orphan Drug, and UI Health gave CellTrans all of its rights and obligations in 2017.[30] Under the Orphan Drug Designation program, medications and biologics used for the diagnosis, treatment, or prevention of a rare sickness or condition—that is, one affecting fewer than 200,000 persons in the US—are designated as orphan drugs.[31]

The FDA governs human allogeneic islets taken from dead donors as "biologic" products. Allogeneic Islet Transplantation, therefore, necessitates FDA pre-market review and approval in the United States (i.e., clinical trials followed by FDA submission of a Biologics License Application (BLA); Any legal person or organization associated with producing, as well as license applicants who accept responsibility for adhering to establishment and product

requirements, may submit a BLA.[32] After various clinical trials, the FDA provided approval for Donislesel for marketing under Lantidra in April 2021.

PHARMACOLOGY OF DONISLESEL

Mechanism of Action

As a result of variations in blood glucose, the highly controlled, pulsatile production of several hormones by the pancreatic islets controls blood glucose levels. Pancreatic islets' endocrine cells secrete ghrelin, insulin, glucagon, somatostatin, and pancreatic peptide.

Pancreatic peptide reduces pancreatic exocrine secretion, glucagon drives the liver's stored glucose into the bloodstream, insulin facilitates glucose absorption by peripheral tissues, and ghrelin suppresses insulin production. These hormones work together to keep blood glucose levels within normal limits.[33]

Dosage and Administration

DOSE: One 1000 mL infusion bag containing 400 mL of provided volume, comprising no more than 10 cc of approximately packed islet tissue, holds the donislecel. The 1000 mL infusion bag is aseptically linked to a smaller 750 mL bag with 200 mL of volume given for use in washing the 1000 mL bag and line following the transplant to guarantee full islet transfer to the patient.[34] Donislecel should be administered at a minimum of 5,000 IE/kg for the first transplant and 4,000 IE/kg for any further transplants the recipient receives. Although a maximum dosage has not been established, each transplant's packed cell volume may not exceed 10 cc.[34-38]

ADMINISTRATION: Donislecel is administered into the hepatic portal vein using laparoscopic or open surgical (mini-laparotomy) access, or per-cutaneous or trans-venous trans-hepatic access if these are not practical. After the transplant, the patient is observed for safety, immunosuppressive levels, and graft function.[28]

Safety, Tolerability, and Efficacy

SAFETY

Under the CellTrans IND, safety has been investigated in two core investigations (UIH-001 [NCT00566813] and UIH-002(27); Pooled Population; N=30). A year following the final transplant and starting from the original transplant is the major safety follow-up period utilized to assist the CellTrans BLA. The assessment also includes long-term safety. Donislecel displayed a safety profile that was comparable with the recognized hazards of the transplant operation and concurrent drug usage, particularly lengthy immunosuppressive medication use.

In the Pooled Population during the primary follow-up, the most common Treatment-emergent adverse events reported (≥60% of patients) were acne (87%), nausea (83%), anemia (83%), fatigue (80%), diarrhea (73%), abnormal weight loss (73%), headache (63%), elevated transaminases (63%), and vomiting.[60] Diarrhea, anemia, and nausea were the most frequent ≥Grade 3TEAEs (≥20% of patients).[27,39]

TOLERABILITY

Islet transplantation addresses a huge medical need for patients with brittle T1D, helps most patients regain good glycemic control, can slow or even reverse usual secondary T1D complications, enhances patient quality of life, and carries a manageable safety risk.[40,41]

EFFICACY

Two core trials under the CellTrans IND (UIH-001 [NCT00566813] and UIH-002 (23); Pooled Population; N=30) assessed efficacy.

After 1 year following their last transplant, 20 out of 30 patients (67%) in the pooled population were insulin-independent, and 19 out of 30 patients (63%) met the composite effectiveness goal. In the Pooled Population, additional efficacious measures such as the hypoglycemia (HYPO) score, fasting and postprandial blood glucose, and fasting and post-prandial C-peptide also showed a significant improvement a year following the last transplant.[27] The persistence of gains in glycemic control over time is noteworthy. Patient demographics (age and sex) had no discernible effect on long-term effectiveness.

Indication of Use

For the management of people with brittle type 1 diabetes mellitus (labile diabetes; brittle T1D) in people whose symptoms do not improve with rigorous insulin therapy, Lantidra (donislecel), an allogeneic pancreatic islet cellular therapy, is advised.[42]

DONISLECEL VS CURRENT TREATMENT OPTION FOR TYPE 1 DIABETES

For T1DM, there are several therapeutic approaches. Nonetheless, the principal treatment for type 1 diabetes is still injectable insulin, which comes with varying durations and onsets to maximize glycemic control.[43] Insulin pens and insulin pumps are used to subcutaneously administer insulin into the body. A patient's insulin needs to be modified based on their level of physical activity, food consumption, and acute or chronic diseases. Since this combination resembles the normal insulin pattern, most patients need a mix of long-acting insulin and rapid-acting insulin analogs, which are often taken before meals, to maintain basal insulin levels.[44]

Pramlintide, taken in conjunction with insulin at mealtimes, is the only non-insulin treatment authorized for T1DM(45,46). It delays stomach emptying and decreases the glucagon level after meals. Less than 5% of patients with type 1 diabetes use it.[47]

Some patients with type 1 diabetes have difficulty taking insulin, which can result in serious adverse effects such as hypoglycemia and diabetic ketoacidosis. The most frequent potentially fatal consequence, hypoglycemia, accounts for 4–10% of T1DM fatalities.[44,47]

Studies on immunosuppressive drugs like ciclosporin and other cell treatments like islet transplantation have piqued researchers' intense interest in treating potentially fatal short-term consequences.[48] The main focus of therapy is preventing T-cell activation, as it is believed that T-cells are engaged in the immune system's attack on these beta cells. By changing the immune system's attack on beta cells, this approach may be able to treat type 1 diabetes.

One such cell therapy named Donidlecel(lantidra) recently got approval from the FDA for the treatment of patients with brittle type 1 diabetes after several clinical trials showing promising efficacy:

In a phase 1/2 clinical trial involving ten T1DM patients who had received cell transplants, it was found that when fasting glucose levels were kept below 140 mg/dL more than three times a week and two-hour postprandial values were kept below 180 mg/dL more than 4 times a week without using of exogenous insulin, eight out of ten patients had

achieved insulin independence. Of the 10 patients in each group, none showed signs of full transplant failure for the course of the 15-month monitoring period.[49]

In another phase-3 study, twenty-one T1DM post-cell transplant patients participated in a different phase-3 study that demonstrated substantial glucose control and no hypoglycemia episodes. At the one-year follow-up visit, 19 out of 21 patients stated that they had no severe hypoglycemia episodes and that their HbA1c was still less than 6.5% NCT03791567.[1]

Donislecel treatment was shown to have no notable negative effects.

T1DM needs ongoing monitoring and therapy throughout life. The approval of this novel treatment is encouraging, particularly for patients with uncontrollably brittle type 1 diabetes since it will lower the number of fatalities in these individuals from hypoglycemia.

CONCLUSION

Our review highlights the promising role of donislecel, being sold with the brand name Lantidra in keeping fasting blood glucose and HbA1c levels within target ranges indicates that it may serve as a more effective alternative to conventional insulin injections or pumps for people with brittle type 1 diabetes mellitus. Despite the limitation posed by the high cost of the therapy and limited information about the long-term effect of donislecel, the benefits of donislecel in a substantial proportion of patients in achieving insulin independence are noteworthy. Our review underscores the fact that the landscape of diabetes treatment continues to evolve, the integration of innovative therapies like Donislecel, alongside traditional management strategies, could significantly boost the standard of living for people with type 1 diabetes.

Conflicting Interest: None.

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