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USE OF TEPLIZUMAB IN THE TREATMENT OF TYPE 1 DIABETES MELLITUS: A LITERATURE REVIEW

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Abstract: Introduction: Type 1 diabetes (T1D) is an autoimmune disease characterized by the destruction of the β-cells of the pancreas, resulting in a lack of insulin and hyperglycemia. This prevents the proper storage of glycogen and the absorption of essential nutrients by the cells, requiring the continuous use of exogenous insulin. DM1 is linked to chronic complications such as nephropathy, retinopathy and an increased risk of infections. Although insulin is the main treatment, immunomodulatory therapies, such as Teplizumab, have shown potential. This monoclonal antibody acts on T lymphocytes, slowing disease progression, protecting β cells and delaying the need for insulin. **Method:** This study is a narrative review that analyzed the literature on the use of teplitzumab in the treatment of type 1 diabetes mellitus. Articles were selected from the BIREME, PubMed and Cochrane databases, using the keywords "teplizumab", "treatment", "diabetes mellitus" "type 1". Inclusion criteria included articles in English and Portuguese, published in the last 10 years. Studies with unclear methodology or no relevance to the topic were excluded. In total, 6 articles were selected and analyzed. **Results and Discussion:** Results indicate that teplizumab significantly preserved pancreatic beta-cell function in newly diagnosed children and adolescents, with less need for exogenous insulin. However, there were no improvements in long-term glycemic control. Other research suggests that although teplizumab slows down the progression of the disease and alters the immune profile of patients, its effects are temporary, and the use of the drug can cause adverse effects such as transient lymphopenia and flu-like symptoms. Despite offering initial benefits, such as preserving beta cell function, teplizumab has limitations, such as variability in therapeutic response and the need for continuous treatment. In addition, the high cost and the need for more clinical studies to improve the administration strategy and long-term monitoring are challenges to be overcome. **Conclusion:** The review reinforces the potential of Teplizumab in the treatment of type 1 diabetes, showing that, although promising, further studies are still needed to better understand its effects and immunological mechanisms. The drug can slow down the progression of the disease, but its side effects and the continuity insulin therapy require strict medical monitoring.

INTRODUCTION

Type 1 diabetes (DM 1) is an autoimmune disease that usually manifests itself by the age of 30, predominantly affecting children and adolescents, but can occur in any age group. It is characterized by an absolute deficiency in the production of insulin by the pancreas, which hinders the storage of glycogen in the liver and results in high levels of glucose in the blood, causing hyperglycemia. This condition reduces the cells' ability to absorb amino acids and other essential nutrients, which requires the continuous use of exogenous insulin to control the disease. The condition is caused by the autoimmune destruction of the β-cells of the Islets of Langerhans, with autoantibodies directed against the β-cells, insulin and other structures such as glutamic acid decarboxylase and tyrosine phosphatase, preventing the production of insulin and, consequently, the transportation of glucose into the cells (SARTORELLI; FRANCO, 2003).

Diabetes, especially type 1 diabetes, is a risk factor for the development of various diseases. The chronic complications of DM 1 are the main causes of morbidity and mortality in diabetic patients. Among the most common complications are diabetic nephropathy, systemic arterial hypertension, diabetic retinopathy, as well as greater predisposition to ulcerative lesions and infections (GROSS et. al, 1999).

Insulin plays a central role in the of type 1 diabetes, since patients do not produce endogenous insulin due to the destruction of the beta cells in the pancreas. Much has been achieved with insulin, from the first methods of administration, such as daily injections with longer-acting insulin, to more recent advances, such as ultra-fast-acting insulin and basal insulin. However, it is even more possible to look forward to other treatments for DM 1, such as the use of immunomodulatory therapies like teplitzumab (PIRES; CHACRA, 2008).

Teplizumab is a humanized monoclonal antibody that acts by binding to CD3, an antigen present on the surface of T lymphocytes, and slows down the progression to stage 3 of type 1 diabetes mellitus (DM1). Although its mechanism of action is not completely clear, it is believed to promote partial agonistic signaling, leading to anergy and deactivation of autoreactive CD8+ T lymphocytes, which are responsible for the destruction of pancreatic β cells. This process prevents the autoimmune destruction of insulin-producing cells. In addition, the release regulatory cytokines and the expansion of regulatory T lymphocytes can restore immune tolerance, protecting β cells and allowing insulin production to continue for longer, postponing the need for insulin treatment (SEEWOODHARY; SILVEIRA, 2023).

METHOD

The study is a narrative review carried out in six stages: selection of the topic and elaboration of the research question; establishment of the inclusion and exclusion criteria for the search; evaluation and critical analysis of the included studies; analysis and synthesis of the included studies with interpretation of the results; and presentation of the review.

This article is a narrative review that aims to analyze the existing literature on the possible benefits of using teplitzumab in the treatment of type 1 diabetes mellitus. The search was conducted through the Regional Library of Medicine (BIREME) using the Virtual Health Library (VHL) and included databases such as PUBMED (National Library of Medicine) and Cochrane.

Using the keywords "teplizumab", "treatment", "diabetes mellitus" "type 1", without restricting any criteria, 143 articles were found in the following databases: PubMed (n=115) and Cochrane (n=28). When conducting the search, the inclusion criteria were: English and Portuguese languages, published in the last few years.

10 years, complete and free articles and the exclusion criteria were: publications in PowerPoint (PPT), those without a date, editorials, letters to the reader, letters to the editor without case reports, articles with unclear methodology and publications that did not fit the desired focus. After applying the inclusion and exclusion criteria, 137 articles were excluded.

After excluding the aforementioned publications, we selected 6 scientific articles for analysis. Based on this selection, we classified, compiled and directed the articles according to the objectives of constructing the final article. Subsequently, we synthesized the results found, taking into account the similarity of content.

RESULTS AND DISCUSSION

This article sought to analyze the literature's approach to the real evidence on the use of Teplizumab in the treatment of patients with type 1 diabetes mellitus. Through a careful survey of the literature on the subject, it was possible to note that recent advances in therapeutic approaches for type 1 diabetes are focusing mainly on strategies aimed at modifying the disease, rather than just controlling the symptoms. In this sense, immunomodulatory therapies, which seek to preserve beta cell function, and the use of stem cells to regenerate the pancreas are gaining ground. They also highlight the possibilities of genetic

editing and biomarker therapies for a personalized approach and the potential of tissue engineering and immunoengineering to prevent the autoimmune destruction of beta cells (WARSHAUER et al., 2020).

The PROTECT study, a phase 3, randomized, double-blind, placebo-controlled clinical trial, evaluated the efficacy of teplizumab in preserving pancreatic β-cell function in children and adolescents with newly diagnosed type 1 diabetes. After 78 weeks of using teplizumab, the treated group showed significantly greater preservation of insulin secretion, with higher C-peptide levels than the group that did not use the medication ($p< 0.001$), as well as less need for exogenous insulin. However, there were no significant differences in long-term glycemic control or in the incidence of hypoglycemia (RAMOS et.al, 2023).

Perdigoto et al., 2019, evaluated the long--term impact of teplizumab in the treatment of DM 1 and revealed that patients treated with teplizumab showed a slower progression of the autoimmune disease and changes in the immune profile of treated patients, including changes in the activity of regulatory and effector T cells, suggesting a prolonged immunomodulatory effect of the drug.

Despite preserving pancreatic β-cell function and slowing the progression of the disease in newly diagnosed patients by prolonging endogenous insulin production and reducing the need for exogenous insulin therapy, the beneficial effects tend to be temporary and the use of the drug is associated with adverse events such as transient lymphopenia, due to depletion of T lymphocytes, and flu-like symptoms such as fever, fatigue, headache and myalgia, possibly related to immune activation induced by the drug. Other less frequent but still relevant effects include skin rashes, nausea and transient elevations in liver enzymes, suggesting a potential hepatic impact that requires monitoring (XIAO-LAN MA et. al, 2024).

According to the article by Simran Thakkar et al., 2023, despite immune modulation to slow disease progression, there are several limitations to teplizumab in the treatment of type 1 diabetes, including variability in therapeutic response, limited duration of effect and the need to better identify patients who would benefit most from therapy. Some individuals show a more robust response, with longer preservation of pancreatic β-cell function, while others do not demonstrate significant benefits, suggesting that genetic and immunological factors may influence the results. Furthermore, although teplizumab manages to slow down the progression of the disease, its effect is not permanent, and β-cell function continues to decline over time, raising the need for retreatment or combination therapies. The authors also mention challenges related to the high cost of therapy and the need for more studies to establish the best administration strategy and long-term monitoring.

Thus, Salama et. al, 2024, highlights the need for a deeper understanding of the immunological mechanisms that regulate tolerance and autoimmunity in type 1 diabetes. In addition, immunomodulators should be evaluated in larger clinical trials to ensure their long--term efficacy and safety. The balance between efficacy and safety in the use of these agents is crucial, since inappropriate modulation of the immune system can lead to adverse effects.

Even though it represents a breakthrough in immunotherapy for type 1 diabetes, teplizumab still has barriers that need to be overcome before it can be more widely adopted in clinical practice, such as the high cost of therapy and the need for more studies to establish the best administration strategy and long-term monitoring (SIMRAN THAKKAR et. al, 2023).

CONCLUSION

This literature review highlights the benefits and limitations of using Teplizumab to treat patients with type 1 diabetes mellitus. However, these benefits still questionable as more studies and a greater understanding of the immunological mechanisms impacted by the medication are still needed.

Therefore, the evidence suggests that even with the continued need for insulin therapy, the findings reinforce the potential of teplizumab as a promising approach to modifying the course of type 1 diabetes, although further studies are needed to better evaluate its side effects. Despite these side effects, the authors emphasize that teplizumab is generally well tolerated and that its benefits in slowing down the progression of type 1 diabetes may outweigh the risks in certain patient profiles, provided there is strict medical monitoring.

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