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Review Article

Teplizumab: a new glimmer of hope for type 1 diabetic patients

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ABSTRACT

Teplizumab is the first monoclonal antibody used to delay the onset of stage 3 type 1 diabetes mellitus (DM). It is a highly selective, a CD3-directed monoclonal antibody, given parenterally that was approved in November 2022, for delaying the onset of Stage 3 type 1 diabetes in adults and paediatric patients aged 8 years and older with stage 2 type 1 Diabetes. It binds to the immune cells that destroy the insulin producing pancreatic beta cells and inactivates them thereby leading to decreased rate of reduction in insulin production and subsequently delay in the onset of stage 3 type 1 diabetes.

Keywords: Teplizumab, Monoclonal antibody, Immune cells

INTRODUCTION

Type 1 diabetes, is a chronic illness. It is also known as juvenile diabetes or insulin-dependent diabetes. This is an autoimmune condition where autoantibodies are produced which destroy the insulin producing beta cells of the pancreas and hence the pancreas is unable to synthesize insulin.[1] Insulin is the major hormone that regulates the intracellular use and storage of glucose, amino acids and fatty acids. In diabetes mellitus type 1, there is insulin deficiency leading to alterations in the metabolism of carbohydrates, lipids, ketones and amino acids, most significant of which is hyperglycemia. Prolonged exposure of tissues to elevated concentrations of glucose leads to several pathological changes across various organs in the body, contributing to major complications of diabetes, including premature atherosclerosis, nephropathy, retinopathy, neuropathy, ulceration and gangrene of the extremities.

The exact etiology of type 1 diabetes is still not clear. Typically, the pancreas's islet cells, which produce insulin, are destroyed by the body's immune system. Other possible factors which are implicated may be genetics, exposure to viruses and other environmental factors.[2] Even though type 1 diabetes typically first manifests in infancy or adolescence, it can also strike adults.

The symptoms of Type 1 diabetes mellitus may vary from increased thirst, frequent urination, increased hunger, weight loss, fatigue, weakness to blurred vision. The staging of type 1 diabetes mellitus is given in Table 1.

In order to establish the diagnosis of type 1 stage 2 diabetes, the criteria followed involves: (1) at least two autoantibodies, (2) dysglycemia with oral glucose tolerance test, (3) history suggestive of type 1 diabetes.

The symptoms may sometimes manifest following a viral illness. In some cases, diabetic ketoacidosis (DKA) may be precipitated if type 1 diabetes is left untreated. In diabetic ketoacidosis, there is absence of insulin, hence inability of the body to utilize glucose as a source of energy. The body then starts utilizing other sources like muscle and fat as potential sources of energy. Breakdown of muscle and fat causes an accumulation of ketones in the blood and urine, imparting a fruity odor to the breath. Other symptoms may

include laboured breathing and vomiting. DKA can cause apathy, lethargy, loss of consciousness, and even death if it is not treated timely. DKA is a medical emergency that requires hospitalization and immediate care with insulin and IV fluids.

Table 1: Staging of type 1 diabetes.

Stage 1	Stage 2	Stage 3
Autoimmunity	Autoimmunity	Autoimmunity
Normoglycemia	Dysglycemia	Hyperglycemia
Presymptomatic	Presymptomatic	Symptomatic
Autoantibodies	Autoantibodies	Autoantibodies
No IGT/IFG	IGT/IFG	Very high blood glucose levels

IGT - Impaired glucose tolerance, IFG - Impaired fasting glucose.

Over a period of time, type 1 diabetes complications can affect major organs in the body. These organs include the heart, blood vessels, nerves, eyes and kidneys. Diabetes is a major risk factor for atherosclerosis also, causing both micro and macrovascular complications kidney failure, stroke, heart disease, blindness, blood vessel blockages due to cholesterol plaques, amputations, bypass surgeries, and angioplasty/stent implantation are all frequent complications. Keeping the blood sugar level under control can diminish the risk of many of these complications. Therefore, regular treatment of these patients is imperative, by giving insulin therapy.

For the management of type 2 diabetes a number of drugs are available, some of these increase the secretion of insulin from the beta cells while others increase the sensitivity of target organs to insulin. But even after a lot of research, no cure has been found for type 1 diabetes. Treatment is by regular administration of exogenous insulin and monitoring of blood glucose levels along with diet and lifestyle modification to prevent complications. There are various types of insulin preparations used for the treatment of type 1 diabetes. They vary in their onset of action, duration of action, amino acid sequence in their structure. Some provide basal insulin levels throughout the day while others cater to the peak levels of glucose after food intake.

Also, so far no drug has been developed which can prevent the development of type 1 diabetes. Teplizumab is the first of its kind monoclonal antibody approved by USFDA in November 2022 that is given parenterally to delay the onset of stage 3 type 1 diabetes in adults and paediatric patients aged 8 years and older with Stage 2 Type 1 diabetes.[3]

MECHANISM OF ACTION

Teplizumab is a CD3 (a cell surface antigen present on the T cells) directed antibody. When administered intravenously, it binds to the immune cells that attack pancreatic beta cells and in activates these immune cells. There is an increase in the proportion of regulatory T cells and of exhausted CD8+ cells in the peripheral blood. As a result, the rate of destruction of pancreatic beta cells is slowed down, hence the decline in rate of insulin production is decelerated. Therefore, there is decreased insulin requirement for few years after diagnosis. It does not prevent or cure diabetes, but, delays the onset of stage 3 diabetes. The mechanism of action of Teplizumab has been depicted in Figure 1.

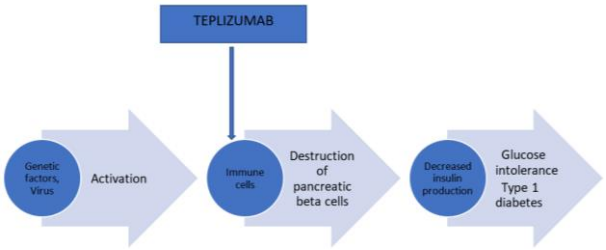

Figure 1: Target for teplizumab for treatment of type 1 diabetes.

DOSAGE AND ADMINISTRATION

The diagnosis of stage 2 type 1 diabetes must be confirmed by documenting at least two positive pancreatic islet autoantibodies in patients with dysglycemia. Type 2 diabetes should be ruled out by appropriate history taking. Teplizumab should not be given in patients with active serious infection or chronic infection. Before starting treatment, complete blood counts and liver enzymes should be obtained. Also, the patient should be pre-medicated with NSAIDs (acetaminophen), an antihistaminic and an antiemetic before each dose of teplizumab for at least first five days of the 14-day treatment course. Teplizumab is administered by IV infusion once daily for 14 days (slow infusion over 30 minutes). Two doses of the drug should not be administered on the same day. It is available as injection- 2mg/2ml (1mg/1ml) as a single dose vial.

THERAPEUTIC INDICATION

It is indicated for the treatment of patients with type 1 diabetes early in the disease. A brief course of Teplizumab leads to decreased rate of decline in insulin production, hence delays progression to stage 3 diabetes.

CONTRAINDICATIONS

Teplizumab is contraindicated in pregnant and lactation, in acute serious infection or chronic infection, severe

lymphopenia and in case of severe hypersensitivity reactions.

ADVERSE EFFECTS

Most common adverse effects of teplizumab are decreased WBC count, rash and headache. There is risk of serious infections, hypersensitivity reaction and Cytokine release syndrome (CRS). Lymphopenia mostly begins to recover after the fifth day of treatment and returns to pre-treatment levels two weeks after course completion. CRS may present as fever, nausea, fatigue, headache, arthralgia, raised liver enzymes. Premedication with antipyretics, antihistamines and antiemetics mitigates these symptoms. throughout the therapy, lymphocyte count and liver enzymes must be monitored regularly.

DISCUSSION

A number of studies have been conducted where Teplizumab has been found to decrease the insulin requirement and delay diabetes in relatives of type 1 diabetics who are at high risk of developing diabetes and has also been found to delay the progress of type 1 diabetes from stage 2 to stage 3.

In Phase I/II randomized control trials, in patients with new onset T1DM, teplizumab slowed the rate of loss of beta-cell function over 2 years of follow-up. Treated patients had better glycemic control and lower insulin requirements, with mild adverse effects. Further, Phase III clinical trials are underway to confirm these results.[4] In both phase I and phase II studies conducted by Skelley et al, it has been demonstrated that C-peptide is preserved (a measure of insulin production),exogenous insulin use is decreased, and glycemic control is improved following a 12- to 14-day teplizumab infusion in patients diagnosed with T1 DM within the previous 6 weeks.[5] In another randomised placebo-controlled trial on participants with type 1 diabetes, the teplizumab group required less exogenous insulin ($p<0.001$) especially in younger individuals and those with HbA(1c) <6.5% at entry.[6]

Lebastchi et al in their study demonstrated that when patients with recent-onset T1 DM were treated with teplizumab, β-cell functions were preserved ($p<0.05$) and the rates of β-cell death were reduced significantly ($p<0.05$).[7] Another study suggested that there is reduced decline in C-peptide and persistent immunological responses up to 7 years after diagnosis of diabetes in individuals who respond to teplizumab.[8]

The data from two different studies conducted on relatives of patients with type 1 diabetes who did not have diabetes but were at high risk for development of clinical disease was studied and it was found that the median time to the diagnosis of type 1 diabetes was 48.4 months in one study and 59.6 months in the second study in the teplizumab group. While in the placebo group, the median time to the diagnosis of type 1 diabetes was 24.4 months and 27.1 months respectively in both the studies; Also, diabetes mellitus was diagnosed in 50% of the participants who received teplizumab in both the studies whereas the disease developed in 72% and 78% of the placebo-treated subjects in both the studies respectively. Hence, it was concluded that Teplizumab delays progression to clinical type 1 diabetes in high-risk individuals and delays onset of diabetes.[9,10] In eight randomized clinical trials involving 866 patients, it was found that Teplizumab was associated with lower insulin use and higher AUC of C-peptide in type 1 diabetic patients than placebo treated subjects. In these trials, a few adverse effects such as lymphopenia, skin and subcutaneous tissue disorders were also reported.[11] Thus Teplizumab is emerging as a promising drug for delaying type 1 diabetes.

CONCLUSION

Teplizumab slows down the rate of destruction of pancreatic beta cells, hence the decline in rate of insulin production is decreased. Therefore, there is decreased insulin requirement for few years after diagnosis. It does not prevent or cure diabetes, but, Teplizumab delays the onset of stage 3 type 1 diabetes in adults and paediatric patients aged 8 years and older with stage 2 type 1 diabetes.

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