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REVIEW

DiaPep277® and immune intervention for treatment of type 1 diabetes

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Abstract Type 1 diabetes is a chronic immune-mediated disease resulting in destruction of insulin-producing β-cells. Several studies have been performed aiming to halt disease progression after diagnosis; to reduce the increased diabetes risk in islet-autoantibody positive subjects; and to prevent the onset of β-cell autoimmunity in subjects genetically at risk but without autoantibodies. Whereas secondary prevention trials failed, trials in newly diagnosed patients have shown partial success in preserving C-peptide. These studies target T-cells and inflammation and make use of antigen-specific immune modulation or stem cell approaches. However, thus far no immune-based therapeutic regimen has cured type 1 diabetes after its clinical onset or has stabilized the decline of C-peptide to achieve the status of an approved drug. This review summarizes immune intervention trials and the current knowledge of DiaPep277® peptide as a form of immune intervention in type 1 diabetes.

Contents

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1. Introduction

Type 1 diabetes accounts for about 10% of all diabetes, affecting approximately 1.4 million people in the U.S., and 10–20 million globally [1,2]. About 40% of persons with type 1 diabetes develop the disease before 20 years of age, thus making it one of the most common severe chronic diseases of childhood [2]. In adulthood, about 10% of patients have type 1 diabetes or LADA (latent autoimmune diabetes of the adult), which is clinical type 2 diabetes with positive islet-reactive autoantibodies [3]. T cells and cellular immune reactivity play a crucial role in β-cell destruction leading to insulin deficiency and the necessity to treat these patients lifelong with insulin. β-Cell loss starts without symptoms at an unknown time before clinical onset and continues thereafter.

Worldwide, the incidence of type 1 diabetes varies. For example the incidence in subjects under 15 years is <0.1 per 100,000 per year in China, rising to 40 per 100,000 per year in Finland [4]. In recent decades the incidence in Finland and Germany has risen, increasing yearly by 5% with a predominance in small children [5]. As this rapid development cannot be explained by genetic factors, environmental changes are thought to account for the rise in incidence. It is reasonable to assume that less susceptible genotypes are sufficient to facilitate the autoimmune process of β-cell destruction [6]. Modified diet, hygiene and altered microbiota are discussed as important potential triggers. However these epidemiological studies cannot prove causality [7].

2. Treatment of type 1 diabetes with insulin

For more than 90 years insulin has been the only medication available to efficiently treat and save subjects suffering from type 1 diabetes. Data from the Diabetes Control and Complication study (DCCT) in the 1980s established that good glycemic control, often achieved by intensified insulin treatment as a golden standard, not only prevents acute symptoms but also reduces the occurrence of diabetes-associated complications resulting from microangiopathy (nephropathy, retinopathy, neuropathy) and macroangiopathy (coronary disease, stroke, peripheral arterial disease).

Data from the DCCT also showed that increased or stabilized C-peptide as a marker of endogenous insulin secretion in type 1 diabetes is associated with fewer diabetes-associated complications including hypoglycemia, thereby indicating that preservation of C-peptide, even if minor, is of benefit for the patient with type 1 diabetes [8]. Similarly, good glycemic control when achieved after diabetes onset can preserve endogenous insulin secretion and should be a goal of treatment in newly diagnosed patients with type 1 diabetes. Patients with hypoglycemic unawareness often have no residual C-peptide and benefit from islet transplantation, which can reduce insulin requirements but also markedly improve hypoglycemic awareness [9]. Because of these observations, it would be desirable to preserve or improve endogenous insulin secretion measured by C-peptide in patients with type 1 diabetes, when they are in need of continuing exogenous insulin treatment [10].

3. Prevention of β-cell loss in prediabetic islet antibody-positive subjects

Secondary prevention trials are performed in subjects who are islet antibody positive and are therefore at increased risk of developing type 1 diabetes. These studies require large-scale screening, as antibody-positive subjects are rarely found in the general population. Accordingly most of these studies screen and recruit first-degree relatives of type 1 diabetes patients. Still, several thousand to ten thousand subjects need to be screened before sufficient subjects could be enrolled for secondary prevention trials.

The diabetes prevention trial (DPT-1) performed in the US in the 1990s aimed at halting progressive β-cell failure before the onset of clinical diabetes by injecting insulin. This trial failed for reasons not well understood, perhaps a lack in the optimal route of insulin administration, dose or timing [11]. However, the oral insulin arm of the DPT-1 showed promising results, namely an increase in insulin secretory capacity especially in the subgroup of insulin autoantibody-positive (mIAA) subjects [12].

Studies with intra-nasally administered insulin in subjects genetically at risk who converted to being antibody positive failed too [13]. Nevertheless, the latter study with intranasal insulin lispro is now being repeated with higher dosing and studies such as PrePoint and Point using oral insulin treatment in subjects at increased risk of diabetes are underway [14]. Other secondary intervention trials, such as ENDIT performed in Europe, treated pre-diabetic islet antibody positive patients with nicotinamide also failed to delay or prevent onset of type 1 diabetes [15].

Although it is reasonable to believe that secondary prevention should be easier to achieve than tertiary prevention as there are more intact β-cells left, the mild therapeutic regimens used thus far have failed to halt β-cell deterioration.