Proceedings of the 2nd International Conference on Modern Medicine and Global Health
DOI: 10.54254/2753-8818/17/20240642

The vaccine of the type one diabetes

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Abstract. At present, the main patients of T1D (type one diabetes) are adolescents and many complications will occur, which is very harmful to the health of adolescents. This article mainly discusses the development and research progress of T1D vaccine. Current potential vaccines include antigen isolation vaccines, APL, monopeptide vaccines and adjuvant vaccines. Among them, autoantigen IA2-based antigen-specific vaccine Hsp65-6IA2P2 protein vaccine and B9-23 APL-based vaccine can effectively minimize the natural diabetes prevalence in NOD mice, DiaPep277 vaccine is based on heat shock protein 60 (Hsp60), which was displayed to maintain C peptide levels in phase I experiments, but phase II trials are not very successful, and are currently entering phase III experiments. The widely used adjuvant alum was combined with the adjuvant vaccine "Diamyd" by GAD65. Diamyd therapy has been successful in adults and has been carried out in phase II studies on kids and teens, with phase III trials currently underway in Europe and the United States.

Keywords: Type One Diabetes, Antigen Specific Vaccine, APL, Monopeptide Vaccines, Adjuvant Vaccines.

1. Introduction

T1D is sometimes referred to as juvenile diabetes and insulin-dependent diabetes, both of which result in high blood sugar levels. It usually appears during childhood or adolescence mainly because of genetic predisposition, the environment like virus, and autoimmune deficiency factors. It is a long-lasting condition brought on by an failure to produce insulin due to the autoimmune damage in beta cell that produce insulin. Pancreas produces hormone insulin, which can lower blood sugar levels. People with T1D may have symptoms like urinating a lot, feeling really tired and weak during the day, having blurry vision, ect. which bring inconvenience to the patients' daily life. So vaccine treatment for T1D is now necessary to be produced.

There are significant complications that have been reported in adolescents with T1D even earlier during childhood. In addition, about 30% of T1DM patients develop terminal renal disease.

High glucose level in the body can cause the red blood cells become sticky and stick together on the wall of blood vessel, forming the clumps which make the blood vessel narrower and lead to the increase in the blood pressure and the broken of the blood vessel [1], the blood leaked will feed the nerves. Then disease like heart and blood vessel disease like Cardiac diastolic dysfunction and nerve damage like peripheral neuropathy can be caused. The nerve damage affects the digestive system, which could cause problems with vomiting, nausea, constipation, or diarrhea. In addition, kidney can also be damaged because of the high blood pressure and cause albuminuria [2].

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Globally, 8.4 million people will have T1D in 2021, predicts a modeling research that was just published in The Lancet Diabetes & Endocrinology, statistics from various epidemiologic research carried out globally show that T1D incidence has been increasing by 2% to 5% annually, and by 2040, it is expected that there will be 13.5 million to 17.4 million people suffering from the disease. Low-income countries have a life expectancy of only 13 years for a 10-year-old child diagnosed with T1DM, while high-income countries have a life expectancy of 65 years. 2.28 per 1000 kids are diagnosed with cancer, compared to 1.24 per 1,000 adolescents (those under the age of twenty old) and 120 per 1,000 adolescents with asthma.T1D also requires patients and families to closely monitor their blood sugar levels using needled lancets or additional tools for monitoring and to frequently administer insulin using syringes, pens, or insulin pumps. These requirements could have an important effect on patients' and families' lifestyle quality. Additionally, there is a considerable influence on public health, which is estimated to have cost the United States a total of a total of 132 billion dollars in 2002.On closer inspection, it can be determined that 5% to 10% of persons with T2D also have gradually worsening T1D as well [3].

Nowadays, people always use insulin pump which is a pump delivers a small amount of insulin continuously as the main treatment of type one diabetes, this traditional treatment has many disadvantages, for instance, patient with T1D need to use this insulin pump for life, and still have risk of DKA (diabetic ketoacidosis) , skin infection and allergic infection. In addition, it also cost a lot that many families cannot withstand such financial pressure. The discovery of vaccines can lead to better treatment of diabetes so that patients may only need to get one or a few doses to completely treat diabetes. Therefore, better preventative measures are becoming more and more necessary to aid in preventing issues with adherence to medication for chronic conditions like diabetes. Consequently, better preventative measures are increasingly required to aid in preventing issues with chronic diseases like diabetes when adherence to medication is a difficulty. Effective vaccines have been discovered through recent approaches that don't involve preventing the beginning of DM before it starts by acting with environmental factors. This article mainly introduces the pathogenic mechanism of T1D and the production principle and current progress of several vaccines for T1D currently under development.

2. Pathology of T1D

There are mainly three pathogenesis of T1D. Genetic factors are the first and foremost factor. T1D is more likely to occur in people who have specific HLA genes. They provide guidelines about how to make the proteins that are required by the immune system to function properly. HLA complex, which situate on chromosome 6p21 and codes for genes of class I, class II , aids the immune system by allowing it to discriminate between proteins manufactured by the own cells of body and those produced by foreign invaders such as virus and bacteria. The capacity of similar auto-antigens to attach can be significantly increased or decreased by antigens present in class II molecules, leading to the development of T1DM. HLA class II has the highest risk haplotypes: DR4-DQA1*03:01-DQB1*03:02 (also known as DR4-DQ8) and HLA-DRB1*03:01-DQA1*05:01-DQB1*02:01 (also known as DR3-DQ2), these alleles account for 30%–50% of genetic T1D risk [4]. They give instructions on how to produce proteins which are essential to the immune system [5].

Second, environment viruses are another factor. Environmental factors that contribute to type 1 diabetes include nutrition, vitamin D exposure, obesity, childhood exposure to enteroviruses, which trigger islet inflammation, and a reduction in the variety of the gut microbiome [6].

T1D can be caused by other factors that have not been proven yet. In T1D, macrophages or dendritic cells (DCs) are able to target and take up beta-cell autoantigens like glutamic acid decarboxylase (GAD), insulin, as well as IA-2, an islet-associated molecule to form antigen-presenting cells (APCs). In APC, antigens are divided into short peptides. Th1 cells are activated when MHC class I and MHC class II molecules are presented to CD4 T cells. When Th1 cells are stimulated, CD8 T cells can morph in cytotoxic T cells (Tc1) which are able to recognize self-peptides on the beta-cell surface that are presented by MHC class I molecules. In the course of the apoptosis process, which is characterized by nuclear chromatin condensation, cytoplasm loss, and the development of surface receptors that cause

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macrophages to consume the apoptotic cell, CD4 and CD8 lymphocytes interact to cause beta-cell death. Fas, IL-1, IFN, TNF, NO, oxygen-derived free radicals, and perforin play a role in activating the caspase pathway and apoptosis through signaling. Additionally, some innate immune cells and macrophages are stimulated by the release of cytokines to further harm beta cells. This positive feedback loop results in the production of additional hazardous cytokines that spread leading to the breakdown of beta cells.

3. Potential T1D vaccine

In addition to increasing antigen-specific Treg cells, getting rid of autoreactive T cells, and preventing immune cell interactions, vaccines can also elicit responses by blocking the conversion of negative Th1 immune responses into positive Th2 immunological responses. The effect of autoimmunity vaccines can be achieved through various methods, for example: immunostimulation, an improvement in the APC's capacity to activate and stimulate regulatory T cells like NKT, Th3, and Treg; a switch from the immune system's destructive (Th1) to more benign (Th2) response to beta-cells, as evidenced by IL-4 and IL-10 generation; eliminating or tolerating autoreactive T cells, stimulating TGF-beta mediated antigen-specific regulatory T cells; avoiding immune beta-cell interaction, or protecting beta-cells from immunologically induced apoptosis, for instance through Fas signaling blocking, are some more strategies.

3.1. Antigen-specific vaccine

By encouraging DCs to produce the IL-10 which is an anti-inflammatory cytokine, which in turn motivates naive cognate Th0 in order to engage in morphogenesis into anti-inflammatory CD4+ Th2 helper cells that in turn secrete IL-10 to suppress the further development of autoreactive Th1 cells and delay the development of potential insulitis, oral administration of islet autoantigens in trace levels have a protective and therapeutic antigen-specific impact. Instead, immature Th0 cells can mature into one of the various regulatory T cell (Treg) subclasses that can inhibit the formation of Th2, Th1, and CTLs, delaying the onset of insulitis, preserving insulin production, and maintaining immunological homeostasis.

IA-2 is a tyrosine phosphatase protein which is referred to as a vital islet antigen for T1D. Studies have suggested that the IA-2 vaccine, either alone or in combination with IL-4/MCP-1 plasmid, can postpone the early and late phases of diabetes caused by autoimmune disorders, offering hope for the future for T1DM sufferers.

His-Hsp65-6IA2P2 protein vaccine is one of the vaccine contain IA-2. There is an animal experiment had been down. Two fusion proteins were given intranasally three times to a four weeks old NOD mice, preserving body weight and normal level of blood glucose and reducing the incidence of diabetes and blood transfusion glenoids. Hsp65-6IA2P2-treated mice had levels of lower IFN-beta and higher IL-10, which is consistent with the proliferation and tolerance of induced spleen T cells.

There is some risk for antigen-specific immunotherapy. The use of antigen-specific vaccine in T1D raises three main issues: development of life-threatening hypersensitivity; acceleration of the illness, resulting in faster beta-cell loss; and induction of 'off-target' autoimmunity. Any preventative or intervention study using an antigen-based method must address the first two of these with prospective individuals before enrollment, whereas the third area of worry is antigen-dependent and will thus be influenced by the trial's design.

3.2. Altered peptides ligands vaccine

Autoantigen-related, MHC-presented snippets of the peptide that have undergone one to several amino acid alterations but still retain the potential to attach to MHC are known as altered peptide ligands (APLs). Antigen-specific Th2 cell responses are started on account of partial activation of autoreactive T cells in response to APL, which could inhibit the progression of the disease. A recent immunological intervention trial recommends giving GAD, insulin, or fragments of insulin in order to establish tolerance to prevent T1D. A modified insulin B chain peptide ligand (B(9-23) APL) was recently recommended for use in intervention trials. There is T cell expansion in reaction to B(9-23) APL in

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patients who have T1D and those who are prediabetic. The B(9-23) APL vaccination can either postpone or stop T1D. Diabetes can be prevented in NOD mice by the B(9–23) peptide, which is an APL of insulin. Two different CD4 epitopes are present in the peptide B(9–16) and B(13–23)), and B(13–23) intersects with B(15–23) of a epitope of CTL. Insulin B(15–23) attaches the Kd class I MHC molecule, with the glycine at position 23 (p9) serving as the additional anchorage and the tyrosine at position 16 (binding in p2) serving as the primary anchor. The peptide's ability to bind to the Kd molecule is eliminated when the tyrosine debris at site 16 is replaced with an alanine or when the C-terminal of B(9-23), or the B(9-21/22) peptide, is truncated. When administered subcutaneously to NOD mice, the B(9–23) APL with alanine substitutions at sites B(16) and B(19) (A16,19 APL) been demonstrated to stop spontaneous hyperglycemia [7].

3.3. Single Peptide Vaccines

DiaPep277 (Andromeda Biotech) is a peptide with 24 amino acids that is stable and isolated from heat shock protein 60 (Hsp60). By activating DCs through exogenous treatment (oral or subcutaneous distribution), a tiny amount of the synthetic HSP60-derived or HSP65-derived fragment of the islet autoantigen Diapep277 can have a defensive therapeutic impact which is antigen-specific. Diapep277 is absorbed by DCs, processed by MHC II molecules, and then presented to new Th0 cells after administration. IL-10, an anti-inflammatory cytokine, which is as well generated by active DCs, transforms naive homologous Th0 lymphocytes into anti-inflammatory CD4+ T cells. Then, these cells discharge IL-10, which inhibits the development of Th1 cells that are self-reactive and postpones the onset of the underlying sexual inflammation. Otherwise, naive Th0 cells might mature to form one of the several regulatory T cell (Treg) subclasses, which could suppress the growth of Th1 lymphocytes and CTL, halt the formation of islet cluster as a result of pro-inflammatory cytokines, and maintain the functionality of beta-cells in T1D [8].

This heat shock peptide could delay the development of T1D in NOD-treated mice by regulating the immune system's attack on beta cells and halting the spread of insulitis in hyperglycemic animals.

The peptide prevents beta-cell death and anti-inflammatory T-cells while sustaining insulin output.

, as shown in a number of phase 2 research. A randomized, double-blind phase II study showed that subcutaneous injection of DiaPep277 patients had a constant average C-peptide concentration after 10 months, while the average C-peptide concentration decreased in placebo-injected patients (0.67[0.33]vs0.43[0.17]U/kg; p=0.042]) [9].

DiaPep277's interaction with their Toll-like receptor 2 activates regulatory T-cells, as demonstrated by additional studies. By stimulating regulatory T-cells, the immune response is redirected away from attacking and toward protecting beta-cells. Consequently, a targeted treatment for type 1 diabetes is made possible without impairing crucial immune processes in mice or people. Remaining C-peptide levels were maintained after administration with DiaPep277 in persons who had just been diagnosed with T1D. The quantity of exogenous insulin treatment needed to keep blood sugar amounts within normal range is not lowered. Phase II trials of immunosuppression in children have not been as successful as expected. The vaccine failed to have a therapeutic effect because C-peptide levels in younger patients remained low throughout the trial. Despite the fact that DiaPep277 was unable to significantly improve treatment for recently diagnosed adult patients with T1D, the vaccine's ability to maintain C-peptide levels in these individuals permitted it to progress to phase III trials. By assessing C-peptide levels, the current phase III experiment aims to evaluate the preservation of the production of insulin in adults.

A phase 3 trial study that is randomized, placebo-controlled, and double-blind showed that the proportion of patients with partial response in the DiaPep277 group was higher compared to the placebo group, achieving partial response in 38.4% of patients in the mITT population compared with 29.3% of those taking a placebo. In both treatment group and the placebo group, the corresponding PP ratios were 41.8% and 30.2%, respectively [10].

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3.4. Adjuvant based vaccine

A single autoantigen may not be the only cause of the onset of T1D, as demonstrated by the expression of antibodies against increasing numbers, and this may be part of the difficulty with single peptide vaccinations that do not entirely suppress human diabetic symptoms.GAD65, insulin, Hsp60, and IA2 are examples of beta-cell autoantigens. Simultaneously inoculating NOD mice with two autoantigens, insulin and GAD, produced a cumulative effect that prevented the onset of diabetes, and this concept was confirmed. In order to overcome multiple diabetic autoantigen problems, it might be beneficial to conjugate autoantigens to adjuvants to increase the level of autoantigen-mediated immunosuppression. Anything that improves the immune response to the antigen it delivers without significantly inducing an immunological response to itself is an adjuvant. Diabetes autoantigen-containing adjuvants can boost the vaccine's immunosuppressive effects while lowering the number of autoantigens needed to elicit the optimal immune response.

Enhance the level of autoantigen-mediated immune suppression by combining the autoantigen with an adjuvant. 'Diamyd' (Diamyd Medical, Stockholm, Sweden) is a vaccine made of the GAD65 protein and contains the widely used adjuvant alum (an aluminum and magnesium hydroxide mixture).Because aluminum salts prefer to trigger a type II immunological reaction rather than immunity mediated by cells, they were utilized to prevent aggravating T cell-mediated beta-cell death.

Phase II trials in children and adolescents have been conducted using Diamyd treatment, which has been effective in adults. Fasting C-peptide levels in the GAD-alum group were 0.332±0.032 mmol/l on day 1 and 0.215±0.031 mmol/l on month 15 according to one phase II, double-blind, randomized, placebo-controlled clinical experiment. In the placebo group, the corresponding values were 0.184±0.033 mmol/l and 0.354±0.039 mmol/l, respectively. Between the first day and the first month, the GAD-alum group showed lower fasting C-peptide levels than the placebo group. The variances between treatment groups that were statistically significant were not notable. After 4 years, the decrease in fasting C-peptide in the GAD-alum group was considerably smaller compared with the placebo-treated group among those who underwent processing within a period of six months after diabetes diagnosis.

Th2 immune response induction is thought to be the cause of Diamyd's activity. Children that received the vaccine showed a rise in GAD IgG4 antibodies, and this is a sign of a Th2 immunological reaction. The release of the anti-inflammatory cytokines IL-5, IL-10, and IL-13 was increased as a consequence of Diamyd's expansion of T regulatory cell numbers, which also increased the number of Foxp3+ T cells. Phase III studies for Diamyd have begun to be carried out in Europe and the United States. Even though Diamyd was beneficial in sustaining lingering insulin production, it is insufficient to help T1D patients achieve euglycemia again. Therefore, it is essential to research fresh vaccination approaches.

There is a 98% chance that 20 g of GAD with aluminum injected twice will have a favorable biological effect, according to a meta-analysis conducted to estimate the efficacy of GAD vaccines. However, in order to achieve clinically appropriate reductions, the biological effect needs to be further explored.

4. Conclusion

This article mainly introduces the pathogenesis of T1D, related complications and some vaccines currently targeted at T1D treatment. With an increase in the number of patients with T1D, the treatment of T1D can not only include dietary advice and insulin injections, but also the development of vaccines is very urgent. At present, most of the research and development of vaccines is based on autoantigen proteins and adjuvants, which will also become the general direction of T1D vaccine research and development in the future. The advent of the T1D vaccine will give hope to more families, and T1D will no longer be a problem in people's lives. Current research also has some shortcomings, such as the vaccine is not effective for a long time, and the current study cannot completely treat T1D. Therefore, it is hoped that future research should improve the timeliness of vaccines.

DOI: 10.54254/2753-8818/17/20240642

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