Advances in Immunotherapy for Type 1 Diabetes

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Abstract. Type 1 diabetes mellitus (T1D) is a common autoimmune disease. Global incidence is on the rise, and traditional insulin injection therapy cannot cure it. With the in-depth study of the pathogenesis of T1D and the progress of medical technology, a large number of innovative therapies are emerging. As one of them, the core of immunotherapy is to regulate the immune system, inhibit autoimmune response, and protect islet β cells. This article reviews the latest research progress of immunotherapy for T1D. Stem cell islet transplantation is relatively safe and effective but still has the risk of rejection. Monoclonal antibodies are effective but cannot be maintained for a long time. Vaccines are relatively simple, but the mechanism is still unclear. At the same time, combined with multiple clinical experimental cases, the development and limitations of immunotherapy at this stage are described in detail, trying to find a new method to break the curse that T1D cannot be cured.

Keywords: Type 1 diabetes, immunotherapy, monoclonal antibody.

1. Introduction

Type 1 diabetes (T1D) is a common autoimmune disease that affects a large number of people worldwide, and the incidence rate is increasing every year. According to the latest statistics from the International Diabetes Federation (IDF), approximately 537 million adults (20-79 years old) worldwide will suffer from diabetes in 2021; it is expected that by 2030, this number will rise to 643 million; and by 2045, it will rise to 783 million. During this period, the world population is estimated to increase by 20%, while the number of diabetes patients is estimated to increase by 46% [1]. T1D brings great trouble to patients and increases the burden on social medical resources. In previous studies, the treatment of T1D mainly relies on insulin injections to maintain blood sugar levels. Although it can control the disease to a certain extent, it cannot prevent continuous damage to pancreatic β cells and abnormal attacks by the immune system and cannot fundamentally cure T1D [2]. As countries around the world conduct more in-depth research on the pathogenesis of T1D, it is found that the immune system plays a key role in the occurrence and development of the disease. Therefore, immunotherapy has become a new strategy for the treatment of T1D. Immunotherapy aims to cure T1D from the root by regulating the function of the immune system, inhibiting autoimmune reactions, protecting pancreatic β cells, and even inducing immune tolerance. In recent years, immunotherapy for T1D has achieved a series of remarkable results. Methods such as stem cell islet transplantation, monoclonal antibody immune tolerance therapy, and vaccines have made significant research progress in the immunotherapy of T1D [3]. However, these immunotherapy methods still face many challenges, such as individual differences in treatment effects, potential adverse reactions, and complex processes that make the methods impossible to mass produce. Therefore, systematically summarizing and analyzing the research progress of immunotherapy for T1D has important theoretical and practical significance for further optimizing treatment plans and improving treatment effects. This article will review the latest research results of immunotherapy for T1D in combination with the three directions mentioned above, and explore its treatment mechanism, current status of clinical application, and future development direction.

2. T1D epidemiology

The incidence and prevalence of T1D vary greatly around the world. According to the "DIAMOND" project initiated by the World Health Organization in 1990, the incidence of T1D in children aged 14 and under in 50 countries around the world from 1990 to 1994 was reported.

According to reports, the incidence of T1D in 100 populations around the world varies by more than 350 times, ranging from 0.1/100,000/year in China and Venezuela to 36.5/100,000/year and 36.8/100,000/year in Finland and Sardinia. In most regions, the incidence increases with age, with the highest incidence in people aged 10-14 years, and the incidence in males is slightly higher than that in females [4]. According to the latest research analysis, in 2021, the number of people with T1D worldwide will be approximately 8.4 million, of which 18% (1.5 million) are under the age of 20. Most T1D patients of all ages are concentrated in 10 countries, namely the United States, India, Brazil, China, Germany, the United Kingdom, Russia, Canada, Saudi Arabia and Spain [5]. The impact of T1D is global and extremely unevenly distributed, so the development of new treatments is extremely necessary.

3. T1D pathological features

3.1. Pathogenesis and Influencing Factors

T1D occurs because the beta cells that produce insulin in the pancreas are destroyed by autoimmune CD4 and CD8+ T cells and macrophages that infiltrate the islets. Current studies have shown that the pathogenesis of this disease involves two aspects: genes and environment. Among the genetic influences, the human leukocyte antigen (HLA) gene located on chromosome 6 is closely associated with T1D, contributing about half of the familial genetic factors of the disease. Secondly, the insulin gene located on chromosome 11 is the second most important genetic susceptibility factor, contributing to about 10% of genetic susceptibility. There are other related genes (screening found that there are at least 15 related genes), such as one allele of the cytotoxic T cell-associated protein-4 (CTLA-4) gene; the type 22 protein tyrosine phosphatase non-receptor (PTPN22) gene; the intercellular adhesion molecule (ICAM) gene. Among the environmental influences, the most concerned are viral infections, such as enterovirus, rotavirus, rubella virus, etc [6]. Genes are closely linked to the risk of disease, while environmental factors play an important role in inducing the occurrence of disease. The two interact and jointly promote the occurrence of disease.

3.2. Diagnosis

Currently, the diagnosis of diabetes is based on blood glucose indicators. The confirmed diagnosis indicator is based on the fasting blood glucose (FPG) value after 8 hours of fasting, FPG greater than or equal to 126mg/dL (7.0mmol/L) or the 2-hour blood glucose value during the 75g oral glucose tolerance test (OGTT) greater than or equal to 200mg/dL (11.1mmol/L) or the glycated hemoglobin (HbA1c) value greater than or equal to 6.5% (48 mmol/mol) [7]. However, since T1D can cause rapid changes in blood glucose levels, the glycated hemoglobin value detection effect is not as good as the first two methods [8]. If you want to distinguish between type 1 and non-T1D, the C-peptide level (AUC) indicator is very important. It can better distinguish long-term diabetes. Because in the early stages of T1D, the body can still produce insulin, so there is a blind spot in C-peptide detection [9]. Therefore, to date, there is no single indicator that can clearly distinguish between T1D and non-T1D. Differentiating between types of diabetes requires more clinical manifestations. For example, the differences in manifestations among different patients. Children often show symptoms of polyuria, polydipsia, and weight loss, and about one-third will experience diabetic ketoacidosis. The onset of adult patients is more diverse and may not show typical symptoms of children, which makes the diagnosis of T1D in adults more challenging [8]. At the same time, age at the time of testing, duration of insulin treatment, and body mass index (BMI) are also very important references. In the combined diagnosis, age diagnosis has the strongest discriminant ability, followed by insulin treatment duration, and BMI is relatively weak [10].

4. Research progress in immunotherapy

4.1. Stem Cell Islet Transplantation

4.1.1 Principle

Pluripotent stem cells (PSCs) have the characteristics of unlimited proliferation and undifferentiation (can differentiate into almost any organ or tissue). The two types of human PSCs (hPSCs) currently under research for clinical application are embryonic stem cells (ESCs) and induced PSCs (iPSCs) [11]. Stem cell islet transplantation therapy has made great progress in the past decade. Its core principle is to utilize the differentiation potential of PSCs (such as iPSCs or chemically induced pluripotent stem cells CiPSCs) to induce them to differentiate into functional pancreatic β cells in vitro. This process refers to the formation of pluripotent stem cells during embryonic development from endoderm, to pancreatic endoderm, to endocrine cells, and finally to pancreatic islet cells [12-14]. The pancreatic β cells are then transplanted into the patient to restore insulin secretion function.

4.1.2 Case study

Deng Hongkui's team in China completed the world's first clinical trial of cell islet transplantation for the treatment of T1D, demonstrating the potential of this therapy in terms of safety and effectiveness. In 2023, a 25-year-old female patient with T1D received an autologous CiPSCs-differentiated islet cell transplant. 75 days after the operation, she was completely independent of insulin treatment, her HbA1c dropped from 8.0% to 4.76%, and her blood sugar target time (TIR)increased from 43.18% to more than 98%, with the efficacy remaining stable for more than 1 year [15]. In addition, Vertex Pharmaceuticals Incorporated of the United States launched VX-880 allogeneic stem cell islet therapy. In a 1/2 clinical trial, 11 out of 12 patients completed the treatment and all achieved HbA1c < 7.0% (2 patients died, both of which were unrelated to VX-880 treatment) [16].

4.1.3 Effectiveness assessment

Based on the above two cases, stem cell islet transplantation therapy has significant effects in the short term: patients' blood sugar control is improved, insulin dependence is reduced or even eliminated, and some cases achieve functional cure. At the same time, long-term effectiveness still needs to be verified. For example, Deng Hongkui's team only has one year of observation data and still needs to be continuously tested, and safety needs to be upgraded. For example, the two deaths in Vertex's VX-880 are said to be unrelated to treatment but still need to be questioned. Overall, this method is extremely effective at the current stage, and clinical trials have shown good treatment effects and high safety.

4.1.4 Problems

Stem cell islet transplantation still has many shortcomings, and the main problems are concentrated in the following points. Although stem cell islet transplantation can induce the generation of β cells, it is still different from endogenous β cells and it is difficult to be exactly the same. Secondly, allogeneic stem cell islet therapy still has the risk of immune rejection. According to existing experiments, it was found that different transplantation sites have different treatment effects, and the best transplantation site should be found. Finally, this treatment method is time-consuming, complex, and costly, and it is difficult to mass produce, and no method has yet left the laboratory.

4.2. Monoclonal Antibodies

4.2.1 Principle

At present, the mainstream monoclonal antibody (mAb) therapy is divided into two categories: depleting mAb and non-depleting mAb. The principle of depleting mAb is to temporarily deplete T cells and B cells, thereby delaying the development of β-cell autoimmunity. The principle of non-depleting mAb is to neutralize cytokines, thereby inhibiting the inflammatory environment of

pancreatic lymph nodes (PLN) and pancreatic islets, and regulating the properties and activities of various immune effector cells [17].

4.2.2 Case study

Teplizumab is a humanized Fc-mutated anti-CD3 monoclonal antibody that can cause a transient increase in the percentage of CD4+Foxp3+T cells throughout the body, thereby promoting the secretion of anti-inflammatory cytokines such as transforming growth factor-β and IL-10, inhibiting the activity of effector T cells, thereby restoring immune balance and preventing autoimmune reactions from destroying pancreatic β cells [18]. Table 1 summarizes three experiments in recent years that evaluated this drug from different perspectives [19-21].

Table 1. Summary of clinical trials

The name of the experiment	Sample	Method	Result
Newly diagnosed T1D patients (AbATE study)	Patients: New-onset T1D (within 8 weeks of diagnosis) Sample size: 52 in the Teplizumab group, 25 in the control group	Open-label, randomized controlled trial Two courses of treatment: 14-day intravenous injection of Teplizumab at diagnosis and 1 year later Dosage: Each course is 14 days. Day 1 dose is 51μg/m2; Day 2 is 103μg/m2; Day 3 is 206μg/m2; Day 4 is 413μg/m2; Days 5-14 are 826μg/m2	The decrease in C-peptide in the Teplizumab group was reduced by 75% 45% of patients in the Teplizumab group had lower baseline HbA1c and used less insulin
Protégé Study (1-year results)	Patients: New-onset T1D (within 12 weeks of diagnosis) Sample size: 209 14-day full-dose group, 102 14-day low-dose group, 106 6-day full-dose group, 98 placebo group	Double-blind, randomized, placebo-controlled Different dose regimens: 14-day high/low dose, 6-day high dose Administration method: 14-day full dose group, 14-day intravenous injection, cumulative dose of about 9034μg/m2; 14-day low dose group, 14-day intravenous injection, cumulative dose of about 2985μg/m2; 6-day full dose group, 6-day intravenous injection, plus 8-day intravenous placebo, cumulative dose of about 2426μg/m2. All treatments were performed once at baseline and 26 weeks	5% of patients in the Teplizumab group discontinued insulin, AUC was better
Prevention Study of Relatives at Risk	Participants: Relatives at high risk for T1D (≥2 autoantibodies and impaired glucose tolerance) Sample size: 44 in the Teplizumab group, 32 in the placebo group	Double-blind, randomized, placebo-controlled Single 14-day intravenous injection of Teplizumab Dosing method: 51μg/m2 body surface area on day 0, 103μg/m2 on day 1, 207μg/m2 on day 2, 413μg/m2 on day 3, and then 826μg/m2 daily from day 4 to day 13	In the Teplizumab group, the median time to progression was delayed by 2 years (48.4 months vs. 24.4 months) The risk of diabetes diagnosis was reduced by 59% (HR=0.41)

In addition, the second method, CTLA-4-Ig fusion protein (Abatacept), is also a common choice. Its principle is to bind to the B7 molecule (CD80/86) of antigen presenting cells, block its interaction with T cell CD28, and inhibit T cell activation [22]. According to clinical trials, among 112 subjects (Abatacept treatment group and placebo group 2:1), the decline of β-cell function in the Abatacept treatment group was delayed by about 9.5 months at 36 months, and the Hb1A1c value continued to be lower than that of the placebo group [23].

4.2.3 Effectiveness assessment

The short-term effect of monoclonal antibody treatment is obvious, especially for early-stage disease or high-risk groups. Teplizumab is the first FDA-approved drug that can delay the onset of

disease by about two years. The AUC and HbA1c data show a good trend and obvious effect; however, the long-term efficacy of Teplizumabz treatment is limited, and most patients still need insulin treatment in the end, and the β-cell repair effect on confirmed patients is weak. At the same time, it can be seen from the above table that this method has some disadvantages. In addition, CTLA-4-Ig fusion protein also has the effect of delaying β-cell failure (delayed by about 9.5 months), but there are few clinical data to correctly judge its effectiveness. In general, the monoclonal antibody method is more effective and has certain clinical data support.

4.2.4 Problems

Among monoclonal antibody therapies, only Teplizumab is currently approved by the U.S. Food and Drug Administration (FDA) on the market, and the treatment method of Teplizumab is highly limited and is only suitable for stage 2 T1D patients, while most patients are already in stage 3. In addition, this method is unstable and has adverse reactions. Problems such as rashes have been reported in clinical trials. At the same time, this method cannot maintain the therapeutic effect for a long time, and most patients still need insulin injections. The cost of treatment is high. Teplizumab is priced at $194,000 per course of treatment (14 days of infusion) in the United States, making it difficult to popularize.

4.3. Monoclonal Antibodies

4.3.1 Principle

The core principle of vaccine treatment for T1D is to achieve the therapeutic purpose by regulating the immune system and inhibiting the autoimmune response. The most common method is to transform the Th1 (cellular immunity) immune response into the Th2 (humoral immunity) immune response.

4.3.2 Case study

The principle of DiaPep277 (heat shock protein) vaccine is to induce autoimmune downregulation of Th1 effector cells and activate Th2 cytokine conversion to reduce damage to β cells [24]. Based on the effect of heat shock protein peptide DiaPep277 on β cell function in children and adults with new-onset T1D, data from two prospective, randomized, double-blind phase II trials showed that the AUC of both children and adults decreased after treatment; in the children group, patients with low HLA risk who received 1 mg DiaPep277 had stable C-peptide levels within 13 months, while patients with low HLA risk who received placebo had a significant decrease in AUC at 7, 13, and 18 months (P=0.016). The decrease in AUC in the adult group after treatment was smaller than that in the children. At 18 months, the AUC of the placebo group decreased (P=0.0425), and the AUC of the 2.5 mg DiaPep277 group decreased (P=0.0024). In the HbA1c test, the baseline range for pediatric patients was 7.7-8.05% and for adult patients was 6.6-7.9%, with overall high levels in both groups at 7 months and beyond. There were no significant differences in HbA1c between treatment groups or at 13 and 18 months compared to baseline HbA1c [25]. The GAD-alum vaccine is similar to DiaPep277 in principle and also has a Th2 immune bias. In a multicenter, randomized, double-blind, placebo-controlled Phase III clinical trial, 334 newly diagnosed T1D patients aged 10-20 years (fasting C-peptide level > 0.3 ng/mL, GAD65 autoantibody positive, and diagnosis time < 3 months) participated in the experiment and were divided into four dose groups: 111 patients received 4 subcutaneous injections of GAD-alum (20 μg/time); two-dose group: 108 patients received 2 GAD-alum + 2 placebos; and placebo group: 115 patients received 4 placebos. The injection time points were 1, 30, 90, and 270 days (four-dose group) and 1, 30 days (two-dose group). Changes in stimulated AUC after mixed meal tolerance test until 15 months. The experimental results showed that the AUC of all groups showed similar decreases at 15 months (four-dose group vs. placebo group, P=0.13; two-dose group vs. placebo group, P=0.20; combination group vs. placebo group, P=0.10) [26].

4.3.3 Effectiveness assessment

Vaccine therapy has limited effects. DiaPep277 (heat shock protein) is not effective. According to data, it has little effect on children and even less effect on adults. It still needs improvement and more experimental verification. GAD65 vaccine performed well in Phase III clinical trials, with a significant decrease in AUC values and fewer adverse reactions. This vaccine is more reliable.

4.3.4 Problems

The mechanisms of DiaPep277 and GAD in this process have not been fully understood, and there are hidden risks. In addition, T1D involves multiple antigen responses, and a single target vaccine may not be sufficient to completely suppress autoimmunity, and the therapeutic effect is not obvious. This method may lead to a decrease in the Th1 immune effect and a decrease in resistance to other diseases.

5. Future Development

At this stage, there have been major breakthroughs in the pathogenesis of T1D, and a deeper understanding of immunology has been achieved, so it is possible to develop new treatments that will provide scientific, effective and safe options for the cure of T1D; however, there are still some problems with immunotherapy for T1D. Stem cell islet transplantation is currently the most promising method, such as the excellent performance of VX-880 in 1/2 clinical trials, but this method requires the use of immunosuppressants. VX-264 is currently being tested to solve this dilemma. Now a single therapy cannot achieve the ideal therapeutic effect. Combination therapy can intervene from multiple aspects. Early suppression of disease onset plus mid-term regulation of immune response can often achieve better efficacy. For example, combining polyclonal regulatory T cells (Tregs) with interleukin-2 (IL-2) (clinical trial number: NCT02691247) There are many combination therapies currently under study, and a complete cure for T1D will no longer be a fantasy.

6. Conclusion

As a global high-incidence disease, T1D has shown an increasing incidence rate over time. An efficient and safe treatment method is extremely important at this time. This article discusses three of the most cutting-edge T1D immunotherapy methods at this stage, which can let readers understand the latest trends in T1D immunotherapy; Stem cell islet transplantation has made great progress, and has shown high efficiency and high safety in clinical trials. It is also the most promising method to completely cure T1D; Teplizumab, as an FDA-approved monoclonal antibody drug, can protect β cells, bringing clinical drug treatment of T1D into a new era. Although there are limitations in its use, the application prospects it has shown still make it further studied and improved; the emergence of a hundred vaccines has brought a low-cost treatment method into the public eye, but the mechanism and risks mean that this method still needs some time to study. The emergence of these new methods makes it possible to cure T1D, and patients no longer need to rely on insulin; in the future, the prevention and reversal of T1D will also become possible.

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