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Immunomodulatory Strategies and GAD65 Therapy in Type 1 Diabetes

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Abstract. Type 1 diabetes mellitus (T1D) is a chronic autoimmune disease characterized by the destruction of pancreatic β cells by the autoimmune system, which is common in children and adolescents. Current treatment still mainly relies on exogenous insulin, which is difficult to achieve a radical cure and cannot prevent the progression of the disease. Therefore, the development of immunomodulatory therapies targeting the cause has become a research focus. This article systematically reviews the pathogenesis and typical symptoms of T1D, focusing on the analysis of immunomodulatory treatment strategies including anti-CD3 monoclonal antibodies (such as teplizumab), low-dose IL-2, and anti-TNF-α, and their efficacy in regulating autoreactive T cells and inducing regulatory T cells. The article specifically discusses antigen-specific treatments targeting GAD65, such as GAD-alum immunotherapy, which has shown the potential to protect residual β cell function in people with specific genetic backgrounds (such as HLA-DR3-DQ2). Mechanistic studies have shown that GAD65 treatment can induce Th2 and Treg immune deviations and inhibit inflammatory responses. Despite the limitations of efficacy differences and individual responses, GAD65-related therapies have broad prospects in the context of precision medicine and are expected to serve as an effective supplement for the treatment of T1D.

Keywords: Type 1 Diabetes, Immunotherapy, GAD65

1. Introduction

Type 1 diabetes mellitus (T1D) represents one of the most prevalent chronic conditions affecting children and adolescents. Worldwide, individuals with T1D make up roughly 5% to 10% of all diabetes cases with Finland exhibiting the highest incidence rate among nations [1,2]. The development of T1D is influenced by both genetic predispositions and environmental triggers, with its primary mechanism involving an autoimmune response that mistakenly targets pancreatic β cells, leading to a complete lack of insulin production. Patients experiencing an absolute deficiency in insulin secretion typically exhibit symptoms like increased urination, excessive thirst, heightened appetite, and weight loss. Additionally, some individuals may encounter less common signs, including tiredness, vision disturbances, and skin irritation. In more severe instances, this condition can result in acute complications, such as ketoacidosis [3]. Thus, carrying out detailed studies on the

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causes of T, Thus, carrying out detailed studies on the causes of T1D, identifying efficient therapeutic approaches, and investigating preventive measures are of great importance.

Nowadays scientific research advances for T1D are thought to be insufficient to support the cure of the disease [4]. Currently, the treatment of T1D is still dominated by insulin therapy [5]. This means that patients are still dependent on long-term continuous exogenous insulin administration [5]. In addition, advances in insulin formulations and delivery methods over time are having a positive effect. Insulin pumps and continuous glucose testing systems have played an important role in improving both glycaemic control and patient quality of life [5]. However, insulin formulations are subject to market price fluctuations, thus causing financial stress for T1D patients [6]. In addition, another major limitation of insulin therapy is reflected in tight glycaemic control [7]. It is difficult to accurately return the blood glucose levels of patients receiving insulin monotherapy to healthy normal levels [7]. Many emerging therapeutic and preventative approaches to T1D are coming to the forefront of public attention with advances in technology and understanding of the factors associated with the disease, relative to traditional insulin therapy. The focus of these anticipated new therapies varies. In terms of insulin, new sources of insulin production and potential alternatives are two major research directions [5]. On the immunomodulatory side, protection of endogenous beta cells is the main goal [5]. For example, an important recent advance involves the use of monoclonal antibodies (mAbs) to effectively maintain normal beta cell function [5]. Among the mAb that have been investigated, therapies involving anti-CD3 antibodies such as teplizumab (humanised anti-CD3 monoclonal antibody) have shown significant potential in treating T1D by modulating the immune response that leads to beta cell destruction [8].

Glutamic acid decarboxylase (GAD65), the dominant beta-cell autoantigen in T1D pathogenesis, shows therapeutic potential for T1D [9]. Our paper systematically synthesizes the current understanding of GAD65 antigen therapy in diagnosed T1DM, focusing on three main aspects: the symptoms and the mechanism of T1DM, the immune modulation therapy and the emerging targets and advanced modalities in GAD65-based immunotherapy for T1D. By integrating mechanistic insights with clinical evidence, this study aims to provide a possible treatment for future research, emphasizing how GAD65-targeted approaches could complement broader immune modulation strategies in the era of precision medicine.

2. Symptoms and mechanisms

The hallmark symptoms of T1D typically consist of polyuria, polydipsia, polyphagia, and weight loss. Additionally, some patients may exhibit atypical symptoms such as fatigue, blurred vision, and skin itching. These manifestations primarily stem from the absolute lack of insulin in affected individuals.

As a result of the complete absence of insulin, cells in individuals with T1D are unable to effectively absorb and utilize blood glucose. This leads to elevated blood glucose levels, which in turn cause osmotic diuresis. A significant amount of water is expelled through urine, leaving patients feeling excessively thirsty and prompting frequent drinking, increased urination frequency. Despite having an increased appetite and consuming more food, the body cannot harness glucose for energy. Consequently, it begins breaking down fat and protein reserves to meet its energy needs. This process results in ongoing weight loss and progressive thinness. In severe cases, patients might experience fatigue, blurred vision, and skin itching. Moreover, due to the relatively rapid onset of T1D, some individuals may initially present with diabetic ketoacidosis [10]. This condition manifests as nausea, vomiting, rapid breathing, and a fruity odor in the breath.

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The development of T1D is influenced by genetic predispositions, environmental triggers, and autoimmune responses. While the autoimmune reaction serves as the direct cause, it is modulated by both genetic and environmental factors. Environmental influences play a crucial role in determining the timing and likelihood of disease onset, particularly in genetically susceptible individuals. Genetic factors establish the baseline risk, but the actual incidence remains relatively low.

Genetics significantly contribute to the onset of T1D. Research indicates that specific human leukocyte antigen (HLA) genes are strongly linked to the disease [11]. Certain HLA allele combinations enhance an individual's genetic vulnerability to T1D. Pancreatic β cells are responsible for synthesizing, storing, and secreting insulin. Environmental factors can lead to viral infections, which may directly harm β cells. Furthermore, dietary components like red meat and other animal [12] products could potentially be associated with the onset of T1D. Environmental elements such as viral infections or chemical exposure may provoke an autoimmune response. In this scenario, the immune system mistakenly identifies insulin-producing β cells as foreign antigens and targets them for attack. Autoantibodies and immune cells continuously assault β cells, causing their gradual deterioration and eventual loss of function. This ultimately leads to insufficient insulin secretion and the onset of T1D.

3. Immunomodulatory therapy

T1D is an autoimmune disorder characterized by T-cell-mediated destruction of insulin-producing pancreatic β-cells. While exogenous insulin remains essential for survival, immunomodulatory therapies represent a paradigm shift by targeting the underlying autoimmune pathology. This section critically examines four therapeutic pillars: mAbs, antigen-specific strategies, cytokine modulation, and cellular therapies, synthesizing clinical evidence and future trajectories.

3.1. mAbs

mAbs constitute the most clinically advanced immunotherapeutic class in T1D. Anti-CD3 antibodies —notably teplizumab and otelixizumab—exemplify this approach. These agents bind the CD3ε subunit of the T-cell receptor, inducing transient T-cell depletion through Fcγ receptor-mediated clearance while simultaneously promoting regulatory T-cell expansion via TGF-β and IL-10 signaling pathways [13]. This dual mechanism achieves selective modulation of autoreactive lymphocytes without broad immunosuppression.

The landmark PROTECT trial demonstrated that a single 14-day teplizumab course delayed clinical T1D onset by 25 months in high-risk individuals, with 45% remaining diabetes-free at 5 years versus 20% in placebo controls [14]. Mechanistic analyses revealed enhanced exhausted CD8+ T-cell phenotypes and durable TCR repertoire changes in responders [15]. Nevertheless, limitations persist: Cytokine release syndrome occurs in 15% of recipients [16], and Epstein-Barr virus reactivation has been documented with otelixizumab [17]. Current investigations focus on Fc-engineered variants to mitigate side effects and combination regimens with low-dose IL-2 to amplify Treg induction [18].

3.2. Antigen-specific immunotherapy

Antigen-specific approaches aim to restore immune tolerance by targeting β-cell autoantigens. GAD65-alum, leveraging glutamic acid decarboxylase 65, dominates clinical development. Upon subcutaneous or intralymphatic administration, GAD65 is internalized by antigen-presenting cells,

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promoting Th2 polarization and Treg differentiation within pancreatic lymph nodes [19]. This retrains the immune system toward tolerance rather than destruction.

Clinical outcomes reveal nuanced efficacy. The European Phase II trial showed GAD-alum preserved fasting C-peptide by 0.06 nmol/L at 15 months versus placebo (p=0.04), while the innovative DIAGNODE study demonstrated that ultrasound-guided intralymphatic delivery stabilized C-peptide at 0.03 pmol/mL compared to progressive decline in controls [20]. Emerging strategies include proinsulin peptide vaccines now in Phase I trials (PRIME study) and hybrid insulin peptides designed to overcome HLA restrictions [21].

3.3. Cytokine-targeted therapies

Cytokine modulation offers precise immunoregulation. Ultra-low-dose interleukin-2 (IL-2) selectively expands functional Tregs without activating effector T cells, exploiting the Treg's high-affinity IL-2 receptor (CD25). The DILT1D trial established that 0.5 MIU/day elevates Tregs by 30%, though transient NK cell suppression necessitates dose optimization [22]. Simultaneously, anti-TNF-α agents like golimumab have shown promise. The TN-22 trial reported a 0.12 nmol/L improvement in stimulated C-peptide at 52 weeks (p=0.02), potentially reducing islet inflammation [23]. Ongoing studies are exploring synergies with teplizumab to concurrently modulate T cells and inflammatory microenvironments.

3.4. Cell-based and emerging strategies

CTLA4-Ig (abatacept), blocking CD28-B7 costimulation, reduced T-cell activation in the T1DAL trial, preserving C-peptide AUC by 59% at 24 months (p=0.002) (Bluestone et al., 2020). More radically, autologous hematopoietic stem cell transplantation (AHSCT) induced insulin independence in 60% of a Brazilian cohort at eight years, though procedure-related mortality (2–5%) restricts applicability.

Adoptive Treg transfer has progressed from polyclonal infusions (25% engraftment in STEADFAST trial) to antigen-specific approaches. Engineered GAD65-reactive Tregs exhibit enhanced pancreatic homing in Phase I studies [24]. Beyond conventional modalities, NLRP3 inflammasome inhibitors (e.g., MCC950) suppress β-cell pyroptosis, while CRISPR-edited PD-1 knockout CAR-T cells show prolonged persistence in preclinical models.

Immunomodulatory therapies have evolved from nonspecific immunosuppression to targeted biologics (anti-CD3), precision vaccines (GAD65), and personalized cellular products (Tregs). While teplizumab demonstrates unprecedented delay in T1D onset, three challenges dominate the field. Biomarker development (e.g., T-cell exhaustion signatures) to identify responders. Rational combinations such as GAD65/IL-2 to amplify efficacy [24]. Long-term safety frameworks for chronic immunomodulation. As articulated by Roep and Tree, the next frontier is durable remission through sequential immunotherapy—halting autoimmunity followed by β-cell restoration.

4. Emerging targets and modalities of GAD65-based immunotherapy of T1D

GAD65 represents one of the key autoantigens, which participate in the autoimmune destruction of the pancreatic -cells in T1D. GAD65 immunotherapies are anticipated to reinstate immune tolerance by the selective suppression of the autoimmune assault on cells. Among the most intensely studied modalities is GAD-alum, in which GAD65 is co-administered with aluminum hydroxide to induce the greatest immunogenicity but with tolerogenic immune deviation.

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Clinical trials have shown that GAD-alum immunotherapy is safe and biologically active. Early subcutaneous administration induced comparatively small immune modulation; however, it did not work in genetically non-selected populations of patients. Most recently (phase IIb), intralymphatic GAD-alum injection, in combination with vitamin D supplementation, has shown promise in genetic sub-groups. Notably, the individuals with the HLA-DR3-DQ2 haplotype have considerably more C-peptide levels of preservation compared to placebo, demonstrating that genetic background is also critical element in response to therapy [25]. The trial has initiated a follow-up trial (DIAGNODE-3) devoted to this subgroup specifically to capitalize on the observed relationship.

There is the intralymphatic administration, which has done better compared to the subcutaneous injections. This is done by in vivo antigen presentation enhancement within lymph nodes, resulting in local, potent immune activation. Intralymphatic GAD-alum immunization enhanced GAD65-specific lymphocyte proliferation and antibody titers than subcutaneous administration [26]. Moreover, GAD-alum intranodal boosters administered years after initial vaccination could re-induce the identical immunological effect, demonstrating that re-dosing can extend or restore immunotherapeutic efficacy.

Mechanistic analyses have revealed that immunotherapy using GAD65 leads to a switch from a pro-inflammatory to a regulatory immune profile. A greater GAD65-stimulated release of interleukins IL-5, IL-10, and IL-13, which are typical cytokines of the Th2 cell and Treg effector functions, was observed in individuals with a clinically relevant response [27]. Conversely, poor responders displayed minimal cytokine deviation; therefore, early immune markers are essential for predicting the therapy's success. Previous researchers who demonstrated the low Th1/Tc1 activity and expansion of GAD65-specific Tregs in treated patients have corroborated these findings. The shifts illustrate immune deviation, which is central to the protective observations seen in a few individuals [28,29].

The advancements in antigen-specific tolerance strategies include the addition of GAD65-based treatment specificity. A low-peptide epitope, P10Sol, was predicted in silico and could provoke tolerance in numerous HLA variants in preclinical humanized mice in Ng et al [30].. These epitope-directed peptide-based therapies are rationally designed. They provide a personalized approach to limiting immune targeting of autoreactive clones with minimal systemic exposure and off-target effects.

Additionally, combination immunotherapy platforms have also been regarded. In this regard, indicatively, Pagni et al. have discovered that a multicomponent DNA vaccine that encoded GAD65, insulin, and IL-10 could prevent the development of the disease in NOD mice both by expanding Tregs and by restricting epitope spreading. These results suggest that β-cell antigens and immunomodulatory molecules may require synergism to achieve a robust immune tolerance [31].

Other promising modalities under development include tolerogenic dendritic cells and nanoparticle delivery of GAD65, which have yielded mixed outcomes in preclinical trials. It seems critical to select co-delivered adjuvants and combinations of antigens. For instance, GAD65 peptide liposomes did not produce any results, but a fusion of insulin fragments and immunoregulatory carriers improved the disease [32].

In conclusion, GAD65-based immunotherapy offers a promising approach to T1D intervention. Its safety profile has been established, and its new modalities—specifically in precision targeting, advanced delivery, and patient stratification—enhance its therapeutic potential. Its efficacy emphasizes the immunologic shift towards a Th2/Treg response while countering the destructive Th1 phenotypes associated with beta-cell damage. Furthermore, integrating mechanistic

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immunology with clinical trial data will be crucial for optimizing these treatments and moving them closer to widespread clinical applicability.

5. Conclusion

This article systematically discusses the typical symptoms and pathogenesis of T1D, and focuses on the latest progress of immunomodulatory therapy in T1D intervention. The core pathological mechanism of T1D is autoimmune β-cell destruction mediated by T cells, which leads to absolute insulin deficiency, thereby causing hyperglycemia-related symptoms such as polyuria, polydipsia, polyphagia and weight loss. Genetic susceptibility (especially HLA genes) and environmental factors (such as viral infection and dietary habits) jointly induce autoimmune attacks on β-cells.

This article analyzes four major immunomodulatory strategies: mAbs, antigen-specific immunotherapy, cytokine targeted therapy and cell therapy. Teplizumab and other anti-CD3 antibodies have achieved remarkable results in delaying the onset of T1D. For example, the PROTECT trial showed that it can delay the onset of T1D by 25 months. GAD65, as a key β-cell antigen, combined with aluminum adjuvant (GAD-alum) treatment showed a good C-peptide retention effect in a specific HLA genetic background, and the efficacy was further enhanced in the treatment of modified administration (such as intralymph node injection) and combined with vitamin D. Precise regulation of cytokines such as IL-2 and TNF-α also has the potential to enhance Treg activity and inhibit inflammation. In addition, Treg cell transfer, CTLA4-Ig, and emerging cell and gene therapies such as CRISPR/CAR-T and nanoparticle delivery are opening up more personalized and lasting treatment pathways.

Authors contribution

All the authors contributed equally and their names were listed in alphabetical order.

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