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Immunotherapy for type 1 diabetes

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Abstract

Type 1 diabetes mellitus (T1D) is a chronic autoimmune disorder in which the immune system attacks insulin-producing β cells in the pancreas, leading to insulin deficiency and hyperglycemia. Despite advancements in treatment, managing T1D remains challenging, with patients experiencing diabetes distress and reduced life expectancy. Immunotherapy offers promising strategies for modifying the course of T1D by targeting the immune system's attack on β cells. A recent highlight is teplizumab, an anti-CD3 monoclonal antibody, which delays the progression of T1D in patients with recent onset by preserving endogenous insulin production. Clinical trials have shown that teplizumab can improve glycemic control and delay the onset of stage 3 T1D for up to two years in at-risk individuals. Other immunotherapies, including targeting B cells with rituximab, have shown potential to preserve β cell function and reduce insulin requirements in recent-onset T1D. Additionally, T cell modulation therapies such as abatacept have been shown to slow the decline in β cell function. Cytokine-directed therapies targeting inflammation have also demonstrated potential in preserving β cell function and improving glycemic control. Combination therapies, such as the use of anti-interleukin (IL)-21 antibodies with liraglutide, may offer synergistic benefits and preserve endogenous insulin secretion. While immunotherapies offer the potential for short-term protection of β cells, ongoing research is needed to refine treatment strategies and identify optimal timing and combinations of therapies. This could lead to safer and more effective management of T1D, potentially reducing reliance on insulin therapy and providing long-term benefits for patients.

Keywords: Type 1 diabetes, immunology, immunotherapy, teplizumab, pancreatic β cells

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HIGHLIGHTS

T cell receptors (TCR) and proteomic analyses are emerging as potential tools for early detection and treatment response monitoring, emphasizing the need for new biomarkers.

Teplizumab has been shown to preserve β cell function and delay Type 1 diabetes (T1D) progression, with significant results in recent trials, and is approved to prevent or delay the diagnosis.

Nonantigen-based immunotherapies, particularly T cell-targeted therapies, have been effective in maintaining β cell function.

Immunotherapies provide short-term protection for β cells; thus, the optimal timing of such therapies is essential for enhancing the response to treatment.

INTRODUCTION

Type 1 diabetes (T1D) is a chronic autoimmune condition marked by the destruction of insulin-producing β cells in the pancreas, resulting in insulin deficiency. Prior to the landmark discovery of insulin therapy in 1921, T1D was typically a fatal diagnosis due to the inability to regulate blood glucose levels. However, the advent of insulin therapy has revolutionized the management of T1D, allowing individuals to maintain glucose control and significantly improve their prognosis. Despite advancements such as newer insulin formulations, insulin pumps, and continuous glucose monitoring, achieving optimal glucose control remains challenging. Individuals with T1D still have a reduced life expectancy compared to the general population and often grapple with the daily management of the condition, leading to diabetes distress[1].

While the precise pathogenesis of T1D continues to be investigated, it is clear that a dysfunction within the immune system plays a critical role in the destruction of pancreatic β cells. The autoimmune process in β cells within the pancreatic islets involves the immune system mistakenly targeting and attacking these insulin-producing cells. This attack is typically mediated by specific immune cells, such as T cells, which recognize β cell antigens as foreign and initiate an immune response against them. This immune response leads to inflammation and destruction of the β cells, ultimately resulting in reduced or complete loss of insulin secretion, culminating in hyperglycemia that progressively manifests as diabetes[2]. Individuals with T1D are also at an increased risk of developing other autoimmune diseases. The most common autoimmune conditions associated with T1D, in order of frequency, include thyroid disease, coeliac disease, autoimmune gastritis, and Addison's disease[3].

The exact mechanisms underlying this autoimmune process are complex and not fully understood, but they involve a combination of genetic predisposition and environmental triggers and immune dysfunction.

FACTORS INFLUENCING T1D

Genetic factors

T1D is primarily influenced by genetic predisposition. Among the 57 presently recognized loci linked to T1D risk, as compiled on http://www.immunobase.org, the human leukocyte antigen (HLA) locus holds the greatest influence, accounting for approximately half of the risk[4]. However, the most particular emphasis is on HLA class II genes, notably HLA-DRB103-DQA105-DQB102 (DR3-DQ2) and HLA-DRB104-DQA103-DQB103:02 (DR4-DQ8), along with HLA class I genes such as HLA-A24, HLA-B18, and HLA-B*39 alleles. Additionally, genes like Insulin Gene (INS), Protein Tyrosine Phosphatase Non-Receptor Type 22 (PTPN22), Interferon-Induced Helicase C Domain-Containing Protein 1 (IFIH1), and Cytotoxic T-Lymphocyte-Associated Protein 4 (CTLA4), located outside the HLA region, also contribute to genetic

susceptibility to T1D[5].

The pathogenic mechanisms through which HLA influences T1D are generally believed to center on antigen presentation. However, it remains unclear whether this occurs primarily through central tolerance/thymic selection or via T cell activation in the periphery[4].

Environmental factors

Research from epidemiological and experimental studies has highlighted specific environmental factors that may contribute to the development of T1D. It is suggested that these factors could influence gene expression through epigenetic pathways, potentially leading to abnormal immune responses and the onset of autoimmunity against pancreatic islets[6].

The increased incidence of T1D in children appears to be more closely associated with lower average temperatures rather than a reduction in the number of hours of sunshine[7]. Furthermore, the diagnosis of T1D demonstrates a seasonal trend, with a higher frequency noted during the colder months of the year[8]. Additionally, a low level of Vitamin D is strongly linked to the prevalence of T1D[9].

There is a growing body of research that supports the association between various viruses and the development of T1D. Enteroviruses have been implicated in the development of T1D through mechanisms that involve initiating autoimmunity against pancreatic β cells[10]. For instance, a meta-analysis by Wang *et al.* (2021) found a significant association between enterovirus infection and an increased risk of T1D across different populations[11]. Furthermore, Cytomegalovirus (CMV), Parvovirus B19, and Human Endogenous Retroviruses (HERV) are also linked to the destruction of pancreatic β cells[12-14]. Additionally, mumps, rubella, rotavirus, enterovirus, and CMV are linked to the initiation of β cell autoimmunity, possibly through molecular mimicry. In vitro studies indicate that these viruses could trigger inflammation markers and alter the expression of HLA class I molecules[15].

New evidence suggests that the Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) virus triggers diabetes by attaching to Angiotensin-Converting Enzyme 2 (ACE-2) receptors during cellular entry, which are abundant in pancreatic β cells and adipose tissue, causing disruptions in glucose metabolism and the destruction of pancreatic β cells[16]. The immune response prompted by SARS-CoV-2 may incite an autoimmune attack on pancreatic islet cells, resembling the development of T1D[17].

These findings highlight the complex interplay between viral infections and autoimmune responses in the pathogenesis of T1D. Ongoing research continues to explore these connections to better understand the disease and develop potential interventions.

Research indicates that the gut microbiota may influence the onset of T1D. Zhou *et al.*'s systematic review in 2020 confirmed a strong link between gut microbiota and the development of T1D[18]. Gut dysbiosis appears to play a role in T1D's development, and a complex interaction between gut microbiota, the immune system, and gut permeability has been identified, though it is not yet fully understood[19]. Abuqwider *et al.*'s 2023 review points out correlations between gut microbiota composition and T1D clinical markers, including a connection between inflammation and gut imbalance in those with T1D[20]. This gut dysbiosis can compromise the integrity of the gut barrier, leading to increased permeability. When the barrier is weakened, immune cells may come into contact with gut microbes and their products, potentially triggering inflammatory pathways. This inflammation can escalate, resulting in the activation of immune cells, which may ultimately lead to β cell autoimmunity[21]. The findings suggest significant

microbiome differences between individuals with T1D and those without, which may affect gut integrity, bacterial movement, inflammation, and glucose control due to an imbalanced microbiome.

Immune factors

In individuals without autoimmune disorders, T cells typically do not initiate abnormal immune responses to self-antigens. This is due to the presence of central immune tolerance and peripheral immune tolerance mechanisms, which ensure proper recognition of self-antigens by the immune system[22]. However, in instances where immune tolerance breaks down, auto-reactive T cells can become activated upon encountering self-antigens. These activated T cells then proliferate and release inflammatory factors, triggering insulitis - a process characterized by inflammation of the pancreatic islets. This ultimately leads to the destruction and loss of β cells, contributing to the development of autoimmune diseases such as T1D[2].

Autoreactive $CD8^+$ T cells play a crucial role in the onset and progression of T1D. Research has shown that when islet-specific cytotoxic T cells, cloned from a patient with T1D, are transplanted into HLA-A2 transgenic Non-Obese Diabetic (NOD)-scid IL2Rγnull mice, which is a novel humanized mouse model, they induce the destruction of β cells[23]. This demonstrates that the immune mechanism underlying T1D is driven by auto-reactive T lymphocytes. Consequently, the presence of persistent auto-reactive T cells in individuals with diabetes is pivotal for the onset of T1D[24].

T cells target the destruction of β cells by recognizing diabetogenic antigen epitopes generated in β cells by anti-islet T cells[25]. Furthermore, research has indicated that auto-reactive T cells present in the pancreatic islets are specific to auto-antigens[26]. Therefore, a distinctive aspect of T1D is the presence of persistent β cell-specific auto-reactive $CD8^+$ T cells in circulation, which play a central role in the development of T1D[27].

T regulatory cells (Tregs) aim to prevent β cell damage by releasing cytokines. Autoreactive B cells are also involved in β cell destruction. They activate autoreactive T cells, which, in turn, release inflammatory cytokines [Interferon Gamma (IFN-γ), Tumor Necrosis Factor (TNF), Interleukin 17 (IL-17)] and engage in CTL-mediated killing. Autoreactive T cells provide signals that aid in the differentiation of autoreactive B cells into plasma cells and the production of islet-specific autoantibodies[2].

Therefore, the destruction of β cells results in the release of auto-antigens and the proliferation of B lymphocytes producing autoantibodies. These autoantibodies serve as dependable biological markers for diagnosing T1D[28].

BIOMARKERS FOR PREDICTING AND MONITORING T1D

Autoantibodies targeting pancreatic β cells are pivotal in predicting the development of T1D. The screening for T1D currently includes autoantibodies such as Insulinoma-Associated Protein 2 (IA-2, also known as Phogrin), Zinc Transporter 8 (Znt8), Glutamic Acid Decarboxylase (GAD), and IA-A2. The detection of a single autoantibody signifies an elevated risk for T1D, while the presence of two or more autoantibodies typically confirms the diagnosis. It is important to note that the absence of islet autoantibodies does not rule out T1D. Similarly, the presence of a single autoantibody does not necessarily indicate autoimmune T1D, particularly in populations with a low prevalence of the disease[29,30].

The predictive value of these autoantibodies is underscored by their ability to identify individuals at risk before the clinical onset of T1D.

Studies have shown that nearly all individuals with multiple autoantibodies will progress to clinical disease. However, the progression rate among those with multiple autoantibodies is highly heterogeneous, emphasizing the need for a nuanced understanding of autoantibody profiles for accurate disease prediction.

C-peptide, a byproduct of insulin production, serves as a crucial biomarker for assessing β cell function in individuals with T1D. Derived from proinsulin, C-peptide levels reflect endogenous insulin secretion. However, its utility is limited in the late stages of the disease when β cell damage has already occurred, resulting in reduced C-peptide levels. The decline in C-peptide levels after stimulated meals specifically indicates an impairment in β cell function[31].

Autoantibodies, on the other hand, are primarily used to predict the risk of developing T1D or to assist in making a diagnosis. Despite their predictive value, autoantibody levels do not correlate directly with disease activity or β cell function.

Following a T1D diagnosis, the measurement of C-peptide, Glycated Hemoglobin (HbA1c), and exogenous insulin is essential for monitoring disease progression. C-peptide levels provide insights into residual β cell activity, HbA1c reflects long-term glucose control, and exogenous insulin requirements indicate the degree of β cell insufficiency[32,33].

Given the limitations of these traditional biomarkers, there is a growing emphasis on identifying immune biomarkers that can provide earlier and more precise insights into the disease process. The discovery of such biomarkers holds promise for reversing or delaying the progression of T1D by enabling more targeted and timely therapeutic interventions[30]. Currently, numerous studies are focused on the discovery of novel biomarkers for T1D, with several potential candidates emerging as promising indicators.

The TCR represents a potential biomarker in T1D. The hallmark of T1D is the T cell-mediated destruction of pancreatic β cells, and considerable research efforts have been directed toward developing TCR-related biomarkers to monitor disease activity. Furthermore, numerous immunotherapy trials targeting T cell function in T1D have shown promise, suggesting that TCRs may serve as biomarkers not only for the presence of T1D but also for monitoring disease progression and response to therapeutic interventions[34].

Proteomic analyses offer a valuable avenue for identifying potential markers of T1D and could provide deeper insights into the progressive decline of β cell function. A mechanistic study has revealed that several proteins exhibit a significant correlation with changes in C-peptide levels, among which Glutathione Peroxidase 3 (GPX3) demonstrates the most pronounced inverse relationship with the fasting C-peptide/glucose ratio[35]. GPX3 is a selenocysteine-containing protein that scavenges reactive oxygen species and plays a critical role in the body's antioxidant systems[36]. It is also involved in regulating metabolism, modulating cell growth, and facilitating signal transduction[37]. In this study, GPX 3 levels were higher in individuals with T1D but decreased as fasting C-peptide/glucose levels increased. This suggests that β cell function decline may be predicted by measuring GPX3 levels. The discovery of these biomarkers constitutes a significant advancement in the quest for novel biomarkers that can aid in the early detection of T1D and the monitoring of treatment responses.

DEVELOPMENTAL STAGES OF T1DM

The natural history of T1D can be classified into three stages as per Insel *et al.*[38]. Figure 1 illustrates these stages:

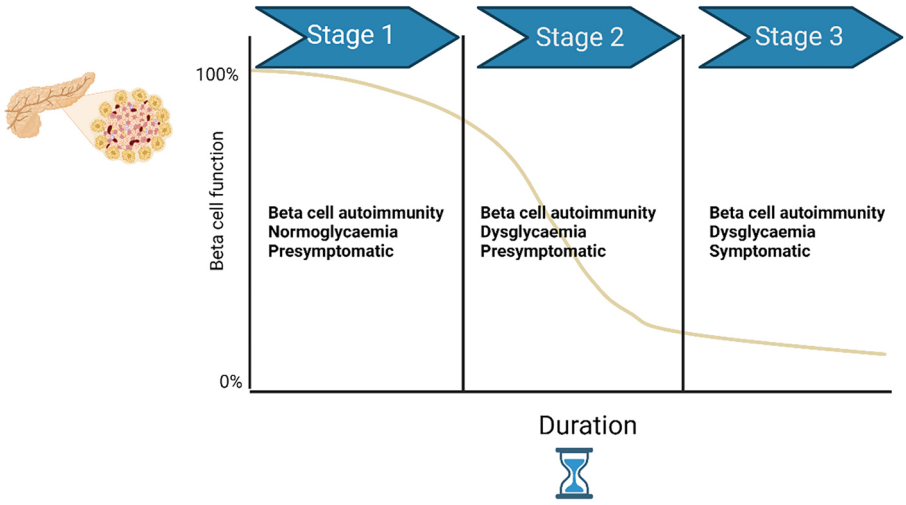

Figure 1. The natural history of T1D. The graph illustrates the progressive decline in pancreatic β cell function over time (yellow line), starting with the Preclinical Stage (Stage 1), where β cell autoimmunity is present without clinical symptoms. This is followed by Stage 2, characterized by IGT without overt diabetes, and culminates in Stage 3, where near-total β cell destruction results in symptomatic T1D. T1D: Type 1 diabetes; IGT: impaired glucose tolerance.

Preclinical Stage (Stage 1): Characterized by the presence of diabetogenic autoantibodies targeting pancreatic β cells. Despite the active autoimmune process, β cell function remains unimpaired and there are no clinical symptoms of diabetes.

Pre-diabetes Stage (Stage 2): Persistent autoantibodies may lead to impaired glucose tolerance (IGT), a pre-diabetic condition with elevated but sub-diabetic blood glucose levels. The presence of autoantibodies and IGT does not necessarily manifest in clinical symptoms of diabetes.

Clinical Stage (Stage 3): Transition from pre-diabetes to overt T1D occurs. The autoimmune destruction of pancreatic β cells results in absolute insulin deficiency. This stage is marked by the onset of clinical symptoms associated with hyperglycemia, such as polyuria, polydipsia, weight loss, and fatigue.

Throughout these stages, the appearance of diabetes autoantibodies is indicative of an autoimmune process targeting the insulin-producing β cells of the pancreas. As the autoimmune attack progresses and the number and function of β cells decline, the risk of developing overt T1D increases. Early detection of Autoantibodies in individuals at risk can help identify those who may benefit from close monitoring and preventive interventions[39].

IMMUNOTHERAPY

T1D is a chronic autoimmune disease characterized by the destruction of insulin-producing pancreatic β cells. Patients with T1D require lifelong insulin replacement therapy, but this approach does not address the underlying pathological process. Achieving a complete cure for T1D hinges on halting the autoimmune attack on β cells. The first immunotherapy used in T1D patients was cyclosporin, which primarily targets T cells. In a landmark study by Feutren *et al.* in 1986, treatment with cyclosporin resulted in complete or partial diabetic remission during the treatment course, but the disease relapsed when cyclosporine was stopped[40]. However, lifelong treatment with cyclosporin was not justified due to its blunt immunosuppressive effect and associated risks. Insulin therapy, while relatively safer, still poses challenges in maintaining good glycaemic control. Now, 40 years after this pivotal study, we have novel

immunomodulator drugs that hold promise for altering the course of T1D.

NON-ANTIGEN-BASED IMMUNOTHERAPIES

Targeting T cells

Anti CD3 therapy

Teplizumab

As a disease-modifying treatment for T1D, teplizumab is a monoclonal antibody that has been humanized. It has been modified from muromonab CD3, murine immunoglobulin, to contain alanine substitutions at critical positions, which inhibit Fc binding[41].

Teplizumab exerts a potent affinity for the CD3 E chain, thereby impacting $CD8^+$ T cells that participate in the autoimmune attack of pancreatic β cells[42]. Notably, it is the first drug approved by the food and drug administration (FDA) to halt the progression of T1D stage 3 in adults and children aged 8 years and older[43]. In their first trial examining the effects of teplizumab on newly diagnosed T1D, Herold *et al*. (2002) discovered that a single course of teplizumab preserved endogenous insulin production and improved glycaemic control for up to 12 months post-diagnosis[44]. These results laid the groundwork for subsequent research aimed at finding a cure for T1D. The landmark ABATE trial examined teplizumab's efficacy in new-onset T1D. This phase II study, comprising individuals aged 8 to 30 diagnosed with T1D within the past 8 weeks, randomly assigned participants to receive either teplizumab or a placebo. The teplizumab group received the drug over two weeks, with eligible participants receiving a second dose after 12 months. At the 24-month mark, the treated group exhibited a 75% increase in adjusted average C-peptide Area under the curve (AUC) compared to controls, although HbA1c levels showed no significant difference between the groups. In conclusion, teplizumab effectively maintained C-peptide levels in recently diagnosed T1D patients, with notable improvements seen in the treatment group, while HbA1c levels remained similar between both groups[45].

In the phase 3 study, PROTÉGÉ trial, 516 patients recently diagnosed with T1D (within 12 weeks) were enrolled. They were randomly assigned to receive one of three regimens of teplizumab or a placebo. The treatment groups received teplizumab infusions in one of the following regimens: a 14-day full dose, a 14-day low dose, or a 6-day full dose. These infusions were administered at baseline and again at 26 weeks. After 2 years of follow-up, the study did not meet its primary outcomes related to daily exogenous insulin requirement and HbA1c. However, there was a significant finding: the teplizumab treatment group demonstrated improved C-peptide preservation, especially in those diagnosed with T1D within 6 weeks of the study initiation compared to the placebo group. While the primary endpoints were not met, the preservation of C-peptide levels, as observed in previous studies, suggests that teplizumab may have a role in delaying the progression of T1D[46].

Teplizumab was also found to be effective in individuals who are at high risk of developing T1D. In another phase 2 trial, a 2-week course of treatment with teplizumab among patients who had two or more antibodies positive, family history of T1D, and IGT showed that the progression to stage 3 diabetes could be delayed for 2 years[47].

The integrated analysis of five clinical trials in stage 3 T1D in evaluating the efficacy and safety of teplizumab over the last 20 years showed significantly greater C peptide levels at 1 and 2 years post-treatment in patients treated with teplizumab than in control patients, which implies preservation of β cell function. Additionally, the reduced reliance on exogenous insulin further supports the therapy's effectiveness in delaying disease progression. The typical adverse reactions to teplizumab include

lymphopenia, rash, and headache, which are generally transient. Additionally, there have been reports of cytokine release syndrome (CRS), significant infections, reactivation of Epstein-Barr virus (EBV), and allergic responses, although these are less common[48].

In brief, the consistent preservation of β cell function by teplizumab highlights its significant immunomodulation effect in managing T1D.

Otelixizumab

Otelixizumab is also a monoclonal antibody that targets the CD3 receptor on T cells. It is used to treat T1D and various autoimmune conditions.

The DEFEND-1 study revealed that a 3.1 mg dosage of the anti-CD3 antibody otelixizumab did not maintain C-peptide levels in new T1D patients. After 12 months, the difference in C-peptide levels between the otelixizumab and placebo groups was not statistically significant. Additionally, no notable differences were observed in HbA1c levels or insulin doses[49].

The subsequent DEFEND-2 trial, which included adolescent participants, also showed that otelixizumab did not offer any additional benefits. The treatment was associated with more adverse events compared to the placebo[50]. Moreover, higher doses of otelixizumab were linked to an increased risk of clinical reactivation of the EBV[51].

These results underscore the difficulty in finding the right balance between the potential advantages and risks of immunomodulatory treatments like otelixizumab, especially concerning safety concerns such as EBV reactivation. Further studies are essential to refine dosing strategies and enhance the safety of these treatments for individuals with T1D.

In summary, although both Otelixizumab and Teplizumab show potential in T1D immunotherapy, Teplizumab stands out with FDA approval for T1D prevention and has proven to positively impact β cell function while maintaining a manageable safety profile.

Antithymocyte globulin

Antithymocyte globulin (ATG) consists of cytotoxic polyclonal immunoglobulin G (IgG) antibodies targeting human T cells, typically derived from rabbit serum and utilized as an immunosuppressive agent[52]. Notably, studies have demonstrated its efficacy in inducing remission in non-obese diabetic mice with recent-onset T1D[53]. Interestingly, findings from a phase 2 placebo-controlled, randomized, multicentre trial revealed that ATG treatment (at a dosage of 6.5 mg/kg) within 100 days of recent-onset T1D did not prevent β cell loss over 12 months compared to the placebo group[54]. However, a three-arm study involving ATG, ATG with granulocyte colony-stimulating factor (GCSF), and placebo demonstrated that low-dose ATG (2.5 mg/kg) preserved β cell function and improved HbA1c levels. In contrast, this improvement was not observed in the low-dose ATG/GCSF group[55]. In a small pilot study in children 5-15 years old with stage 2 T1D, low-dose ATG could potentially delay the progression of T1D and preserve insulin production[56]. In brief, some studies indicate potential in preserving β cell function, while others did not observe significant benefits, highlighting the need for more research for further evaluation.

Targeting B cells

Rituximab

The destruction of β cells in diabetes is primarily driven by a T cell-mediated auto-immune process. Additionally, B lymphocytes contribute to this process by presenting antigens and activating T cells.

Rituximab is a chimeric anti-human CD20 antibody that binds to the CD20 antigen on B lymphocytes, resulting in B cell depletion[57].

In a phase 2 study by Pescovitz *et al.*, the role of rituximab in T1D was evaluated. Administering a single four-week course of rituximab to patients with recently diagnosed T1D (stage 3) demonstrated preserved β cell function, lower HbA1c levels, and reduced insulin requirements at one year. However, follow-up with these patients for up to 30 months revealed that these benefits were not sustained. Nevertheless, there was a notable reduction in C-peptide decline by 8.2 months compared to the placebo group[58,59].

It remains unclear if repeated infusion would result in a more prolonged effect on β cell function or if early intervention at the preclinical stage would be more effective.

Co-stimulation modulators

T lymphocytes require interaction with peptides expressed by antigen-presenting cells (APCs) via their T cell receptors, in combination with costimulatory signals, to reach complete activation[60]. By blocking these signals, these could potentially prevent the autoimmune destruction of the β cells in T1D.

Abatacept

Abatacept, a recombinant fusion protein also known as cytotoxic T-lymphocyte-associated protein Ig (CTLA4Ig), plays a pivotal role in modulating the immune response by disrupting T cell costimulatory signals. It achieves this by binding to CD80 and CD86 on APCs, thereby impeding the interaction between CD28 on T cells and its ligands[61]. This inhibition effectively prevents the activation of T cells, contributing to the regulation of immune activity[62].

In the TrialNet Abatacept study, the administration of abatacept over a 2-year period effectively slowed the decline in β cell function among individuals with recent-onset T1D stage 3. This decline was assessed using C-peptide, which serves as a surrogate marker for β cell function. Notably, the beneficial effect persisted for at least 1 year after discontinuation of abatacept infusions or 3 years from the initial diagnosis of T1D. Additionally, HbA1c levels remained lower for up to 3 years in the abatacept group compared to the placebo group. However, the daily insulin requirement between the two groups did not show a significant difference[63].

After this exciting observation, subsequent research was undertaken, which involved patients diagnosed with stage 1 T1D. The study included 212 participants who exhibited two or more diabetes-related autoantibodies and had a familial predisposition to T1D. Abatacept or a placebo was administered for 12 months. It failed to prevent the development of glucose intolerance among individuals at risk of developing T1D, which is the main objective of this study. Meanwhile, the treatment group had a statistically significant difference in the C-peptide area under the curve (AUC) at the 12-month mark, with higher levels of C peptide observed in the group treated with abatacept. Notably, the Abatacept treatment group exhibited a rise in the quantity of naïve T cells while reducing the number of Tregs. This indicates that Abatacept regulates the activation of T cells in individuals with T1D[64].

Alefacept

Alefacept, a fusion protein composed of two lymphocyte function-associated antigen 3 (LFA-3) molecules that are bound to the Fc segment of IgG1, binds to CD2. This protein is most abundantly expressed on effector memory T cells, i.e., $CD4^+$ and $CD8^+$ cells. These cells are believed to be the primary contributors to β cell elimination in T1D. Alefacept depletes T cells through a mechanism dependent on NK cells and disrupts CD2-mediated T cell co-stimulation[65,66].

In the Targeting of memory T cells with alefacept in new-onset type 1 diabetes (T1DAL) trial, patients with recently diagnosed stage 3 T1D received either Alefacept or a placebo in two 12-week courses over 36 weeks. The results showed that Alefacept effectively maintained endogenous insulin production, decreased the exogenous insulin requirement, and notably lowered the chance of major hypoglycemic events by 50% during the 2-year study period[67]. However, the findings were not statistically significant. In T1DAL, there is also evidence of Treg preservation and a rise in the ratios of Tregs to memory T cells. Their finding supports a correlation between hypoproliferative $CD8^+$ T cells and favorable outcomes from research involving immunomodulatory drugs for T1D[68]. Unfortunately, the withdrawal of Alefacept from the market means that it is no longer available for immunotherapy for T1D.

Cytokine directed therapies

Inflammation and pro-inflammatory cytokines are important players in the complex multicellular interactions that occur between immune cells and pancreatic β cells during the development of T1D and are potential immunotherapeutic targets for this disorder[69].

T1D is characterized by an increased concentration of tumor necrosis factor-alpha (TNF-α), which plays a role in the development of an autoimmune response that ultimately leads to the destruction of the β cells[69].

Etanercept

Etanercept, a TNF-α antagonist, has been investigated in a small pilot study involving patients with newly diagnosed T1D. Treatment with Etanercept for 12 weeks resulted in a decrease in Hemoglobin A1c (HbA1C) levels and an increase in endogenous insulin production, indicating the preservation of β cell function[70].

Golimumab

Golimumab is a monoclonal antibody of the IgG1-κ class that targets TNF-α. It has been authorized for the treatment of certain autoimmune disorders.

The T1GER study (officially titled "A Study of SIMPONI® to Arrest Beta-cell Loss in Type 1 Diabetes") involved 84 people, aged 6-21 years, who were newly diagnosed with overt T1D and were randomly given either subcutaneous golimumab or a placebo for 52 weeks. In this study, Golimumab is associated with better endogenous insulin production and reduction of exogenous insulin requirement despite no significant difference in HbA1c levels[71].

Small-molecule inhibitors

Baricitinib, a Janus kinase inhibitor (JAK inhibitor), targets the JAK-STAT signaling pathway within cells. This pathway plays a crucial role in regulating various cytokines and growth factors involved in a wide range of biological processes, including immune regulation[72]. By inhibiting this pathway, JAK inhibitors are effectively used to treat inflammatory and autoimmune diseases[73].

In a recent phase 2 randomized controlled trial (BANDIT), patients with recently diagnosed T1D (stage 3) who received Baricitinib at a daily dose of 4mg demonstrated preservation of β cell function. This improvement was evidenced by an increase in simulated C-peptide levels following a mixed meal test, as compared to the placebo group. Additionally, the Baricitinib-treated group showed lower daily insulin requirements and improved HbA1c levels at the 48-week mark. Continuous glucose monitoring revealed better glycaemic control in the Baricitinib group at weeks 12 and 24, although this effect was not sustained by the end of the study. It has a good safety profile and adverse events were similar to those in the placebo group[74]. Notably, Baricitinib is administered orally, offering greater convenience for patients compared to injectable treatments like teplizumab. These findings highlight the potential of Baricitinib as a therapeutic option for preserving β cell function in T1D patients.

Recent studies have indicated that immune checkpoint inhibitors, which are pivotal in treating a variety of cancers, may also trigger autoimmune conditions, including autoimmune diabetes. Notably, treatments with Nivolumab or Pembrolizumab, which inhibit the PD-1 protein on T cells and enhance the immune response, have been associated with the development of autoimmune diabetes in approximately 60% of cases[75]. Although T1D is a significant adverse effect of these therapies, strategically modulating the same immune pathways might offer a novel approach to induce or reestablish immune tolerance to β cells. This could potentially delay or even prevent the onset of T1D. In this context, PD-1 agonists such as Peresolimab represent a promising avenue for future research in T1D immunotherapy[76].

Combination therapies

Interleukin 21, a cytokine primarily synthesized by T helper cells, is linked to autoimmune disorders, with heightened IL-21 levels detected in both peripheral blood and tissues of individuals with T1D[77]. Hence, inhibiting IL-21 holds promise in mitigating β cell damage. Liraglutide, a Glucagon-like peptide-1 receptor (GLP-1R) agonist, has demonstrated efficacy in preserving β cells by alleviating stress and apoptosis. When combined, IL-21 blockade and Liraglutide administration have been shown to ameliorate hyperglycemia in a mouse model of T1D[78].

In a randomized controlled phase 2 trial, a 54-week regimen of anti-IL21 antibody treatment combined with liraglutide 1.8 mg daily in individuals recently diagnosed with T1D showed significant preservation of endogenous insulin secretion. However, this effect was not sustained upon cessation of the treatment[79].

Antigen-specific immunotherapy

Antigen presentation is a crucial process in which an antigen is presented to the immune system, leading either to activation or tolerance. The exposure of specific antigens to naïve T cells could induce immune tolerance to that antigen. T1D is also characterized by immune dysregulation, accompanied by detectable autoantibodies. Antigens obtained from β cells, when administered in a non-inflammatory state, have the potential to regulate autoreactive T cells, leading to the preservation of β cells[80].

Insulin

Insulin, a crucial autoantigen in T1D, plays a significant role[81]. During the early preclinical stage of T1D, individuals often exhibit elevated levels of insulin autoantibodies[82]. However, recent studies have shown that administering oral or parenteral insulin to patients at risk of T1D does not delay the time to diagnosis of T1D[83-85].

GAD

GAD 65 is a major autoantigen in T1D. In phase 3 trial, treatment with subcutaneous Alum- formulated GAD 65 (GAD alum) in recent onset T1D did not prevent stimulated C peptide decline at 15 months compared with placebo[86]. This is in contrast to previous phase 2 study, where GAD 65 showed efficiency in maintaining residual secretion. One possible explanation is that H1N1 vaccination during the phase 3 trial may have had an impact on the study's outcome[87].

Upon further examination of this research, a correlation has been identified between individuals with recent-onset T1D who possess the DR3-DQ2 haplotype and a notable preservation of C peptide. A similar finding was also observed in another small pilot study that compared subcutaneous *vs.* intratympanic GAD 65 injection[88].

This implies that taking into account HLA information might have a major impact on the assessment of treatment response to ASI in T1D[89].

DNA plasmid encoding proinsulin

A preliminary phase 1 research demonstrated positive outcomes when administering DNA immunization using a proinsulin-encoding plasmid named BHT-3021 to patients diagnosed with T1D within 5 years. This study observed a decrease in the number of proinsulin-reactive CD8 T cells. The C peptide levels remained preserved throughout the course of the treatment[90].

Recent post-mortem studies found that CD8 T cells reactive to preproinsulin antigen constitute a larger fraction of pancreatic CD8 T cells in pancreas donors with T1D and tested positive for antibodies, compared to non-diabetic donors. It supports the hypothesis that the autoimmune cascade may be triggered by antigens from β cells. These findings may further pave the way for designing antigen-specific immunotherapies to regulate immune tolerance against β cells[91,92].

In summary, Antigen-specific immunotherapy (ASI) may restore a self-tolerance immune system targeting pancreatic β cells and ASI remains a promising approach in pursuit of a cure for T1D.

The verdict of current immunotherapies

A 2024 systemic review by Lin *et al.* reported that immunotherapies for T1D have yielded positive results for nonantigen-based immunotherapies[93]. This study discovered that nonantigen-based immunotherapies were associated with the preservation of 2 h and 4 h C-peptide AUC in patients with T1D compared with the controls. This preservation was more significant when the duration of follow-up was over one year. Additionally, these nonantigen-based immunotherapies have demonstrated the potential to decrease daily insulin requirements without increasing the risk of hypoglycemia. Specifically, T cell-targeted therapy and TNF-α inhibitors were markedly effective in preserving the function of β cells, and in reducing the amount of insulin needed daily. Despite these findings, no substantial differences were observed in the HbA1c levels from the baseline when comparing nonantigen-based immunotherapies with control groups. Nonetheless, T cell-targeted therapies did exhibit a difference in fasting plasma glucose levels in comparison to controls[93].

T1D is a complex autoimmune disease characterized by the involvement of multiple immune pathways and autoantigens, leading to the destruction of pancreatic β cells. Its pathophysiology is multifaceted, arising from a combination of genetic predisposition and environmental risk factors, which result in significant heterogeneity in disease progression and treatment response among individuals. Various autoantibodies are

associated with T1D, and the immune-mediated destruction of β cells involves several mechanisms[94]. Consequently, targeting a single immune pathway may not be sufficient to prevent disease progression but may only delay its onset. Once the autoimmune attack begins, the process is often irreversible, underscoring the challenge of effectively preventing and treating T1D.

Although current immunotherapies have shown some success in delaying disease progression, most studies report a parallel decline in C-peptide levels over time in both treatment and control groups, indicating ongoing β cell loss during the immune attack[95]. Recent studies suggest that immunotherapies, particularly teplizumab, are effective in delaying T1D in high-risk individuals. However, early intervention at stage 1 does not appear to significantly delay disease progression compared to intervention at stage 2. Screening the entire population at the preclinical stage (stage 1) and initiating treatment in high-risk individuals would be extremely challenging[96,97].

For immunotherapy to effectively halt the immune attack in T1D, a combination of drugs targeting multiple immune pathways could be beneficial[30]. Combining agents such as teplizumab, which targets T cells, with rituximab, which targets B cells, may enhance the suppression of the autoimmune response. This dual-target approach may hold promise, as it could address different components of the immune system simultaneously. However, such combination therapies come with challenges. Increased immunosuppression could heighten the risk of side effects.

While immunotherapies for T1D offer promise in preserving β cell function, they often involve immunosuppression, which increases the risk of both common and opportunistic infections. While short-term benefits are encouraging, the long-term safety of these therapies remains uncertain. Potential risks, including viral reactivations, malignancies, and autoimmunity, must be carefully considered in conjunction with the potential benefits .

Therefore, careful consideration must be given to the balance between efficacy and safety. It would be interesting to know whether repeated courses of immunotherapy could further reduce the decline in C-peptide levels, a marker of residual β cell function.

In summary, future research should focus on enhancing these therapies, identifying the most suitable candidates for treatment, and investigating combination approaches that could provide more significant and lasting benefits.

As illustrated in Table 1, various immunotherapies have been explored for the treatment of T1D, each with differing mechanisms of action and levels of efficacy. Notably, therapies such as Teplizumab have shown promise in delaying the diagnosis of diabetes.

CONCLUSION AND FUTURE DIRECTION

Current immunotherapies provide short-term protection for β cells, but determining the optimal intervention timing for the best treatment response remains uncertain. Given the diverse nature of T1D, combining therapies may yield better results. Genetic analysis can guide treatment decisions, minimizing side effects. Extensive research has deepened our understanding of T1D, leading to innovative management approaches. Despite advancements like hybrid closed-loop systems and artificial pancreas technology, achieving optimal glycaemic control remains a challenge. Teplizumab's potential for delaying T1D progression brings hope, but new therapies must balance safety and effectiveness to replace century-old insulin treatments.

Sann *et al. Metab Target Organ Damage* 2024;4:37 | https://dx.doi.org/10.20517/mtod.2024.37

Table 1. Summaries of immunotherapies for T1D; mechanism, efficacy and side effects

Immunotherapies	Mechanism	Stages of T1D	Efficacy in T1DM	Remarks	Side effects	References
Cyclosporine	Non-specific immunosuppressant	Stage 3	-increase rate and length of diabetes remission		Nephrotoxicity and increased risk of cancer	[40]
Teplizumab	Anti-CD3 Immunotherapy	Stage 2 and 3	-improved C-peptide -HbA1c levels and insulin doses were reduced -prevented or delayed the diagnosis of diabetes by at least 2 years	FDA approved to halt the progression of T1DM stage 3 in adults and children aged ≥ 8 years	lymphopenia, rash , headache , CRS, infection, EBV reactivation	[43]
Otelixizumab	Anti-CD3 Immunotherapy	Stage 3	-preserved residual β cell function -delayed the rise in insulin requirements		higher dose of otelixizumab increased the risk of unwanted EBV reactivation	[49,50]
ATG	Cytotoxic Polyclonal IgG targeting T cell	Stage 3	-Preserved C-peptide response and reduced Hba1c, Preserved Insulin production		serum sickness, CD4 lymphocyte decrease, CRS, fever, influenza-like symptoms and rash	[55]
Rituximab	B cell-targeted therapy, Anti-CD20 immunotherapy	Stage 3	Reduction in C-peptide decline but not sustained		Infection, lymphopenia, Progressive multifocal leukoencephalopathy, CRS	[59]
Abatacept	CTLA-4	Stage 3	Slowed the decline of β cell function, and improved HbA1c	The beneficial effect continued for at least 1 year after cessation of monthly abatacept infusions over 2 years	Infusion-related reactions, Infections, dizziness, nausea, high BP	[63]
Alefacept	Co-Stimulation Modulator , Ig fusion protein comprising two LFA-3 molecules bound to Fc portion of human Ig G1 , Inhibit CD2 receptor	Stage 3	Preserved C-peptide secretion at 4 h Decreased exogenous insulin requirements Lower major hypoglycemic events rate	Drug is no longer available Did not meet the primary outcome but met secondary outcomes	Injection site reactions, infections, hepatic injury, EBV infection /reactivation,	[67]
Etanercept	TNF-α antagonist	Stage 3	Lower HbA1c Increase in C-peptide Increase in total daily insulin dose		Infection, lymphoma and other malignancies	[70]
Golimumab	Monoclonal Ab of IgG1-k class that target TNF-α	Stage 3	Increase endogenous insulin production Reduce exogenous insulin use		Infections, Injection-site reaction, and hypoglycemia	[71]
Anti-IL21 and liraglutide	IL-21- cytokine from T helper cells, immunomodulatory effect Liraglutide (GLP-1 Agonist)	Stage 3	Preservation of β cell function	this effect did not sustain upon cessation of treatment	Gastrointestinal side effects related to Liraglutide such as nausea, constipation , and diarrhoea	[79]
Baricitinib	JAK inhibitor	Stage 3	Improve C-peptide secretion Improve HbA1c Reduce exogenous insulin	Oral tablet	Similar to placebo in study Know SEs – shingles, increased risk of infection, DVT and PE	[74]

Oral insulin		Stage 1	Did not prevent the deterioration of β cell function	Safe	[84,85]
GAD	Autoantigen in T1DM	Stage 3	Did not prevent C-peptide decline	Comparable to placebo	[87]
DNA plasmid encoding proinsulin	DNA immunization using proinsulin-encoding plasmid named BHT-3021	Stage 3	C-peptide remained preserved	No drug-related AEs	[90]

This table summarizes the main findings of the various immunotherapies discussed above. T1D: Type 1 diabetes; FDA: food and drug administration; EBV: epstein-barr virus; ATG: anti-thymocyte globulin; CRS: cytokine release syndrome; IgG: immunoglobulin G; CTLA-4: cytotoxic T lymphocyte-associated antigen 4; LFA-3: lymphocyte function-associated antigen 3; TNF-α: tumor necrosis factor-alpha; Ab: antibody; IL-21: interleukin 21; GLP-1: glucagon-like peptide-1; GAD: glutamic acid decarboxylase; T1DM: type 1 diabetes Mellitus.

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