Exploration of Immune Targets for Type 1 Diabetes and Latent Autoimmune Disease Immunotherapy

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Abstract: Type 1 diabetes (T1D) is an autoimmune disease that destroys pancreatic beta cells, which produce insulin in the islets of Langerhans. The risk of developing T1D is influenced by environmental factors, genetics, and autoantibodies. Latent autoimmune diabetes in adults (LADA) is a type of T1D that is genetically and phenotypically distinct from classic T1D. This review summarizes the accumulated information on the risk factors for T1D and LADA, and immunotherapy trials that offer insights into potential future combined therapeutic interventions for both T1D and LADA to slow the rate of islet cell loss and preserve beta cell function. Future research should also focus on improving intervention doses, conducting more thorough examinations of intervention responders, and/or combining minimally effective single-target immunotherapies to slow the rate of islet cell loss and preserve beta cell function.

Keywords: type 1 diabetes, LADA, immunotherapy, islet cells

Overview of Diabetes

Diabetes is a metabolic disease defined by hyperglycemia caused by deficiencies in insulin production, action, or both.1 Diabetes long-term complications include retinopathy, which can lead to vision loss; nephropathy, which can lead to renal failure; peripheral neuropathy, which can lead to foot ulcers, amputations, and Charcot’s joints; and autonomic neuropathy, which can lead to gastrointestinal, genitourinary, and cardiovascular symptoms, as well as sexual dysfunction. Atherosclerotic cardiovascular, peripheral arterial and cerebral vascular disease are more common in diabetic patients. In persons with diabetes, hypertension and anomalies in lipoprotein metabolism are frequently detected.1,2

Diabetes is classified into four types or categories by the American Diabetes Association: type 1 diabetes, type 2 diabetes, gestational diabetes mellitus, and diabetes caused or associated with specific conditions (such as neonatal diabetes and maturity-onset diabetes of the young), exocrine pancreas diseases (such as cystic fibrosis and pancreatitis), and drug- or chemical-induced diabetes (such as with glucocorticoid use, in the treatment of HIV/AIDS, or after organ transplantation).2

Immune system modulation is the goal of immunotherapy, a method that has proved effective in treating autoimmune diseases. However, immunotherapy treatment for T1D and LADA has had a low success rate. In this review, we summarize the accumulated information on the risk factors for type 1 diabetes and latent autoimmune diabetes in adults and immunotherapy trials that offer insights into potential future combined therapeutic interventions for both T1D and LADA to slow the rate of islet cell loss and preserve beta cell function. We highlight the most important immunotherapeutic techniques that have been evaluated thus far, with an emphasis on distinguishing traits.
**Type 1 Diabetes**

Type 1 diabetes (T1D) affects more than 1.2 million children and adolescents worldwide. T1D is an autoimmune disease characterized by the destruction of immune-mediated pancreatic beta cells in the islets of Langerhans. Although T1D can occur at any age, it is most common in children and young adults. For those with T1D, daily insulin injections are necessary to maintain a healthy blood glucose level and are required for people with T1D to survive. Insulin therapy does not cure T1D or completely avoid complications, the use of insulin has revolutionized T1D management. Apart from the acute complications of hypoglycemia (abnormally low blood glucose) and diabetic ketoacidosis (DKA), poor metabolic control results in poor growth and the onset of vascular complications at an early age.

**Risk Factors for T1D**

The risk of developing preclinical or clinical T1D is influenced by environmental exposures and genetic predisposition. It is suggested that gluten diet, cow milk, vitamin D intake, gut microbiota, viral infections (enteroviruses, Coxsackieviruses), drugs (streptozotocin, pentamidine, and antibiotics), and epigenetic modifications all these factors play a role in T1D development.

**Risk Gene for T1D**

According to genome-wide association studies (GWASs), T1D is a polygenic disease with approximately 50% genetic risk attributable to the HLA-DR-DQ haplotypes of the major histocompatibility complex (MHC) region of human leukocyte antigen (HLA) class II (HLA), which are responsible for the presentation by B lymphocyte cells, dendritic cells, and macrophages to cluster of differentiation CD4+ T lymphocyte cells.

Most non-HLA-associated genes identified by GWASs are involved in immune regulation and function (insulin, protein tyrosine phosphatase non-receptor type 22 (PTPN22), interleukin 2 receptor subunit alpha (IL2RA), SH2B adaptor protein 3 (S12H2B3), protein tyrosine phosphatase non-receptor type 2 (PTPN2), cytokytic T-lymphocyte associated protein-4 (CLTA4), interleukin 18 receptor accessory protein (IL18RAP), c-c motif chemokine receptor 5 (CCR5), interferon induced with helicase C domain 1 (IFIHI1), a cluster of differentiation 226 (CD226), protein kinase c theta (PRKCO), interleukin-2 (IL-2), BTB domain and CNC homology 2 (BACH2), ubiquitin associated and SH3 domain containing A (UBASH3A), a regulator of G protein signaling 1 (RGS1), T-cell activation Rho GTPase activation protein (TAGAP); insulin production and metabolism (Erb-B2 receptor tyrosine kinase 3 (ERBB3); protection from beta cell apoptosis (tumor necrosis factor alpha-induced protein 3 (TNFAIP3). The UK Biobank Affymetrix axiom array data was recently used to validate a genetic risk score (GRS) that used 67 single nucleotide polymorphisms (SNPs) (14 HLA DQA1-DQB1 SNPs, 21 other HLA SNPs, and 32 non-HLA SNPs) for newborn screening and future T1D incidence. T1D GRS considerably enhanced the discrimination of T1D patients from T2D and control participants. These data have made it possible to create GRS that could be used to identify those who are at high risk. Although identifying GRS can determine their lifelong risk for developing a disease, it cannot forecast those who have the preclinical disease and are experiencing the destruction of their beta cells.

**Immune Pathogenesis**

Islet autoimmunity in T1D manifests as persistent hyperglycemia and low c-peptide due to permanent loss of more than 70% of beta cell mass months to decades before the clinical disease. Blood glucose, HbA1c, and c-peptide were the only way to diagnose T1D before the discovery of the underlying immunological pathogenesis and biomarkers to identify those who have the disease.

T1D is characterized by the presence of specific autoantibodies (AAbs) for beta cell antigens as well as insulitis. Several other additional autoantigens have also shown their presence and are recognized in human T1D as shown in Table 1.
Table 1 Islet Autoantibodies to Pancreatic Insulin-Producing Cells Secreted in T1D

<table>
<thead>
<tr>
<th>Autoantigen</th>
<th>Expression</th>
<th>Subcellular Location</th>
<th>Function</th>
<th>References</th>
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<td>Carboxypeptidase H/E</td>
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<td>Secretory granules</td>
<td>Proinsulin to insulin processing</td>
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<td>Chromogranin A</td>
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<td>Secretory granules</td>
<td>Precurser of several biologically active peptides</td>
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<td>Glutamic acid decarboxylase 65</td>
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<td>Gamma-aminobutyric Acid Synthesis</td>
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<td>Islet cells, neurons</td>
<td>Synaptic like microvesicles</td>
<td>Gamma-aminobutyric Acid Synthesis</td>
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<td>Glucose-regulated protein 78</td>
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<td>Protein folding</td>
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<td>Mitochondria</td>
<td>Protein folding</td>
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<td>Insulinoma- associated antigen-2β</td>
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<td>Islets amyloid polypeptide (pPIAPP)</td>
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<td>Glucose homeostasis</td>
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<td>Islet- cell antigen 69</td>
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<td>Nucleus</td>
<td>DNA binding transciptional factor</td>
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<td>Pancreatic duodenal homeobox protein 1</td>
<td>Beta cells</td>
<td>Nucleus</td>
<td>Role in pancreas development, beta cell differntiation, and function</td>
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<td>Neuroendocrine cells</td>
<td>Filaments</td>
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<td>Secretory granules</td>
<td>Glucose homeostasis</td>
<td>[25,27,28]</td>
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<tr>
<td>Prolyl 4 hydroxylase subunit β</td>
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<td>Endoplasmic reticulum</td>
<td>Formation and rearrangement of disulfide bonds</td>
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<tr>
<td>Tetraspanin-7, Glima 38</td>
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<td>Plasma membrane</td>
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<td>Urocortin-3</td>
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<td>May regulate insulin secretion</td>
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<tr>
<td>Zinc transporter 8</td>
<td>Beta cells</td>
<td>Secretory granules</td>
<td>Zinc uptake in beta cell secretory granules</td>
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Disease onset. The adoption of this staging classification will give T1D a standardized taxonomy, aid in the creation of treatments and the planning of clinical trials to prevent symptomatic disease, advance precision medicine, and offer a structure for an optimized benefit/risk ratio that will influence regulatory approval, reimbursement, and the adoption of
interventions in the early stages of T1D to prevent symptomatic disease. Islet-targeting autoantibodies that target glutamic acid decarboxylase 65, insulinoma-associated protein 2, insulin, and zinc transporter 8 are all proteins linked to secretory granules in beta cells and are all biomarkers of T1D-associated autoimmunity that are discovered months to years before symptoms appear. These markers can be used to identify and study the risk of developing T1D.

At 5, 10, and 15 years of follow-up in the Colorado Diabetes Autoimmunity Study in the Young (DAISY), the Finnish T1D prediction and prevention (DIPP), and the German BABYDIAB and BABYDIET studies, the progression rates of T1D following seroconversion were 43.5%, 69.7%, and 84.2%, respectively. Understanding the immune mechanisms of T1D has made it possible to identify individuals who are more likely to experience clinical disease and to create a novel treatment that aims to delay the onset and reverse the effects of the disease.

In recent years, the T1D Biomarker Working Group and its accompanying Core for Assay Validation (www.t1dbiomarkers.org) have been dedicated to transferring promising candidate biomarkers from the discovery arena to confirmation and validation testing through a collaborative and coordinated approach. T cell-related biomarkers would significantly speed up disease progression monitoring and the evaluation of T1D intervention therapy. Due to the extremely low frequency of diabetogenic T cells in peripheral blood, the low avidity contacts between autoreactive T-cell receptors (TCRs) and the HLA peptide complex, and the significant disease heterogeneity, this research has proven to be challenging. However, recent advances in single-cell technologies are making it possible to characterise diabetogenic T cells in high-dimensional phenotypic, transcriptional, and epigenetic detail. This might eventually lead to the discovery of accurate and sensitive immunological biomarkers.

Research Resources such as the Network for Pancreatic Organ Donors with Diabetes and Juvenile Diabetes Research Foundation (nPOD; http://www.jdrfnpod.org/) provide an organized framework for obtaining tissues from subjects with T1D or at risk of T1D, allowing for direct study of islet-infiltrating T cells, islet autoantigen reacting T-cells. Human peripheral autoreactive T cells reacted to epitopes that showed posttranslational changes such as disulfide bonds in insulin, islet-derived T cells with hybrid insulin peptide, fusions of proinsulin c-peptide with islet amyloid polypeptide (IAPP). Islet-infiltrating T lymphocytes that specifically target proinsulin peptides. The B9–23 specific T cells of the islets responded to proinsulin, highlighting the relevance of proinsulin-specific T cells in the islet microenvironment. CD4 T cells identify epitopes generated by the covalent cross-linking of proinsulin peptides to other peptides found in cell secretory granules. These hybrid insulin peptides (HIPs) are antigenic to CD4 T cells. T cells that target hybrid peptides explain how immunological tolerance is disrupted in T1D. Understanding the TCR repertoire of pathogenic T cells in T1D may allow for their isolation and use as surrogate biomarkers of drug efficacy in individuals receiving immune therapies.

**Latent Autoimmune Diabetes in Adults**

The pathogenesis and clinical manifestations of LADA are extremely diverse. Beyond the distinction between classic T1D and LADA, the extensive heterogeneity of autoimmune diabetes is evident. It differs from classic T1D/T2D in terms of genetic background, autoimmune response, rate of decrease in pancreatic islet function, and clinical metabolic characteristics. It is characterized by genetic, phenotypic, and humoral variability, encompassing varying degrees of insulin resistance and autoimmunity. Although these patients did not require insulin at the time of diagnosis, they are believed to have a slowly progressing form of autoimmune diabetes with serum immunological markers of T1D.

The primary current diagnostic criteria for LADA include adult-onset diabetes (>30 years at diagnosis), the presence of diabetes-associated autoantibodies, and the lack of insulin demand for at least 6 months following diagnosis.

The genetic distribution and phenotypic traits of the various LADA groups were related to the GADA level. From the lowest GADA quartile to the highest, a significant trend toward reduced insulin secretion and metabolic trait values was observed. Therefore, LADA patients with high GADA concentrations resembled but were not identical to, patients with T1D, while those with low GADA concentrations resembled patients with T2D. Although the risk genotypes for HLA-DQB1 and protein tyrosine phosphatase non-receptor 22 (PTPN22) were elevated in LADA, they were substantially less prevalent than in T1D.

LADA accounts for 2–12% of all diabetes patients, with wide variations based on ethnicity, the autoantibody used for screening (most frequently an autoantibody against glutamic acid decarboxylase [GADA]), and the method of diagnosis.
The human and an established rat model (LEW.1AR1/Ztm-IDDM) of LADA pancreas demonstrate variations in immune cell infiltration, as well as a shift in the ratio of macrophages to CD8 T cells in the islet infiltrate, owing to an increase in Interleukin 1 beta (IL-1β) and a reduction in tumor necrosis factor-α. In LADA, Interleukin 10 (IL-10), proliferating cell nuclear antigen (PCNA), and insulin expression rose, but caspase 3 gene expression decreased, the underlying pathophysiology in human and rat LADA pancreases was identical. LADA is a milder type of autoimmune diabetes in individuals of a late age.47

Risk Factor for Latent Autoimmune Diabetes in Adults

In the first genome-wide association study of LADA, GWAS signals indicate that LADA is a late-onset form of T1D, albeit with genetically attenuated potency of key T1D-associated HLA haplotypes and also with a genetic component similar to T2D. Functional studies look at how the glycolytic regulator PFKFB3 is placed at the nexus of autoimmune and metabolic diabetes.48 Independent effects of MHC class I reported in T1D were not observed in LADA, indicating that the association of MHC class I may be a genetic discriminator between LADA and childhood-onset T1D.49 Recent research has confirmed the genetic relationship between LADA and both T1D and T2D, as well as the subtype-specific signatures in the HLA and a novel LADA-specific locus called PFKFB3. GRS, which includes T1D-risk variations, is a useful tool for differentiating diabetes subtypes and identifying patients who are insulin-dependent in fast-developing states. Although genetic evidence supports the existence of LADA, more research is needed to fully determine its role in the diabetes spectrum.50

The Nord-Trøndelag Health Study (HUNT) genotyped 60 SNPs known to be associated with T1D or T2D, including 14 tag SNPs for HLA haplotyping in 120 patients with T1D, 126 LADA, and 1090 T2D. Genetic heterogeneity of LADA is linked to varying degrees of autoimmune activity and is distinguishable from both T1D and T2D. Most strongly associated HLA haplotypes for T1D were significantly associated with patients with LADA, but primarily with LADA with high anti-GAD levels. There were no connections between LADA and non-HLA T1D loci. Tetraspanin-8 (TSPAN8) and the fat mass and obesity-associated (FTO) were two T2D-related genes that were generally associated with LADA, but primarily in patients with low anti-GAD LADA levels.51 The researchers investigated the relationship between altering beta-cell function in patients with latent autoimmune diabetes in adulthood and GAD autoantibody (GADA) titers. Initial GADA titers in LADA patients identified subjects with varying degrees of persistent autoimmunity and disease progression. Low GADA titer LADA patients shared T2D patients’ metabolic characteristics and decreased beta-cell function.52 In two large population-based studies (the Swedish case-control study and the Norwegian HUNT Study), obesity and overweight are linked to an increased risk of LADA, especially when combined with a family history of diabetes.53 BMI was higher in LADA than in T2D but lower in T1D. GAD antibody titer in LADA correlated negatively with BMI and c-peptide secretion. Beta cell function from the intravenous glucose tolerance test (IVGTT) in LADA was 228% higher than in T2D but 35% lower than in T1D. LADA had insulin sensitivity comparable to T2D but 41% higher than T1D.54 The systematic and meta-analysis study found polymorphisms of protein tyrosine phosphatase N22 (PTPN22), Insulin, transcriptional factor 7-like 2 (TCFL2), and variants of cytotoxic T-lymphocyte antigen-4 (CTLA-4) as risk factors for LADA.55,56

Furthermore, consumption of processed red meat was associated with an increased risk of LADA particularly in people with a family history of T1D or high-risk HLA genotypes (HLA-DQB1 and HLA-DRB1).57 The family history of T1D, as well as a family history of T2D, was linked to an elevated risk of LADA.58 Being overweight, physical inactivity, smoking, low birth weight, sweetened beverage consumption, and alcohol use are all associated with an increased risk of LADA.59-61 LADA may be avoided by making the same lifestyle changes as T2D, such as losing weight, increasing physical activity, and quitting smoking.

During the 7-year follow-up period, 119 (56.1%) of the 212 LADA patients required insulin. In the first year after diagnosis, high GADA titers, BMI ≤ 25, ZnT8 and IA-2 positive, and sulfonylurea medication significantly enhance the development of insulin demand in LADA patients. The distinctive gut microbiota and related metabolites of LADA patients are linked to autoantibodies, glucose metabolism, islet function, and inflammatory factors, all of which may contribute to the disease’s etiology.62
Immunotherapy Approaches to Suppress Beta-Cell Autoimmunity

In recent years, various combination therapies that target the many pathways involved in beta cell destruction have been proposed. However, new promising combination therapies, such as those that combine immunomodulators with drugs that stimulate beta cell regeneration to restore normoglycemia, are being developed. In the pancreatic draining lymph node (pLN), a stem-like autoimmune progenitor gives rise to pLN autoimmune mediators. Using single-cell RNA sequencing and clonal analysis, researchers discovered that autoimmune CD8 T cells represent distinct T cell differentiation states and identified factors that drive the transition from a stem-like autoimmune progenitor to the autoimmune mediator in the pLN. Strategies that target the stem-like autoimmune progenitor pool have the potential to be novel and powerful immunotherapeutic interventions for T1D. Targeting the stem-like autoimmune progenitor pool may lead to the development of innovative and potent immunotherapeutic treatments for T1D. Moreover, researchers hypothesized that microneedle intradermal administration of human proinsulin peptide C19-A3 coupled to ultrasmall gold nanoparticles (GNPs) may increase antigen-specific immunotherapy by promoting tolerogenic dendritic cell immunomodulation. Liraglutide, a drug used to promote beta cell regeneration, and immunotherapy based on Phosphatidylserine (PS) in the membrane and encapsulating insulin A and B chains (PSAB-liposomes) shown to reduce hyperglycemia in an autoimmune T1D model with spontaneous onset. Recent data suggest that MBD2 (methyl-CpG-binding domain 2) could be a viable target for developing epigenetic-based T1D therapeutics in clinical settings. Mbd2 deficiency exacerbated the development of T1D in the NOD mice model. Th1 stimulation caused the Stat1 promoter to undergo DNA methylation and induction of MBD2 expression, which then bound to methylated CpG DNA within the Stat1 promoter, allowing MBD2 to maintain Th1 program homeostasis and prevent autoimmunity. By controlling the STAT1-IFN axis, MBD2 functions as a repressor to maintain the homeostasis of the Th1 program in T1D. Moreover, the deletion of Renalase (RNLS), a potential gene for T1D identified by a GWAS, made beta cells resistant to autoimmune destruction in a mouse model of T1D. In diabetic mice, oral pargyline protected transplanted beta cells, by delaying diabetes development. RNLS is a therapeutic target to prevent the loss of beta cells in T1D and a regulator of beta cell susceptibility. However, its precise role in LADA is unknown.

Circulating C-X-C motif chemokine receptor type 5-negative, programmed cell death protein 1-positive (CXCR5−PD-1hi) peripheral T helper (Tph) cells are linked to clinical T1D development. Tph cells are useful biomarkers of disease progression as well as a target for immunotherapy in T1D. A combination of six HLA-DRB1*0401-selective beta-cell peptides was administered intravenously to individuals with this genotype who had just developed T1D at dosages of 10, 100, and 500 g per month for 24 weeks. Treatment resulted in dose-dependent increases regulatory T cells (Treg) expression of the canonical transcription factor FOXP3 and altered expression of the Treg gene, as well as substantial modifications in islet-specific immune responses. Multiple-peptide immunotherapy shows promise as an approach to repair immune regulatory abnormalities key to the pathobiology of autoimmune diabetes in this first-in-human investigation.

Immunotherapy Approaches from Intervention for Prevention of T1D

Despite over a century of insulin replacement treatment, there is still no cure for T1D etiology. Finding the “correct” therapy for the “right” patient at the “right” moment is still an unmet goal in T1D. For those with T1D, disease-modifying treatments continue to be an aspirational goal. Several therapies, including anti-inflammatory medications, and T or B cell-specific immunosuppressants, have been investigated thus far. In addition, a small number of clinical trial data have revealed minor benefits of immunotherapy in T1D summarized in Table 2.

In the Phase 2 study, a single 14-day session of teplizumab (Fc receptor-nonbinding anti-CD3 monoclonal antibody) significantly reduced the development of clinical T1D in high-risk, non-diabetic relatives of diabetic patients with at least two autoimmune and abnormal oral glucose tolerance test. The median delay in diabetes diagnosis was two years. The individuals most likely to respond were those lacking one T1D-associated MHC allele, HLA-DR3, but possessing HLA-DR4, as well as the absence of anti-ZnT8 antibodies (ClinicalTrials.gov Identifier: NCT01030861). Teplizumab is currently licensed in the United States for patients who are at high risk of developing T1D.

Consequently, in multicenter, double-blind, randomised controlled trial T1D patients aged 6–45 years who have just received abatacept (10–1000 mg/kg per dose) intravenously on days 1, 14, and 28 and once a month for a total of 27
infusions for two years. Over two years, co-stimulation modulation with abatacept halted the decline in beta cell function. The positive impact shows that T-cell activation still occurs around the time of T1D clinical diagnosis (ClinicalTrials.gov Identifier: NCT00505375).

Children who had been diagnosed with T1D received daily anakinra for 28 days and were observed for 6 months. Before and after anakinra therapy, blood was taken for microarray analysis. Anakinra-treated patients showed identical HbA1c and mixed-meal tolerance testing (MMTT) responses, but reduced insulin needs 1 and 4 months after diagnosis, and lower insulin-dose-adjusted HbA1c 1 month after diagnosis, compared to controls (ClinicalTrials.gov Identifier: NCT00645840).

In clinical investigations, T1D patients aged 6–45 years were included in a randomized, placebo-controlled experiment. In newly diagnosed T1D, canakinumab (a human monoclonal anti-interleukin-1 antibody) 2 mg/kg (maximum 300 mg) subcutaneous injection monthly for 12 months was proved safe but ineffective as a single immunomodulatory medication (ClinicalTrials.gov Identifier: NCT00947427). In organ-specific autoimmune diseases, interleukin-1 inhibition may be more efficient when used in conjunction with therapies that target adaptive immunity. At a dose of 0.4 mg/kg (maximum dose of 25 mg/dose), twice a week, etanercept (TNF receptor inhibitor) is administered subcutaneously to 18 newly diagnosed T1D patients (11 men and 7 women, ages 7.8–18.2 years). Etanercept therapy reduced HbA1c and increased endogenous insulin production in young individuals with newly diagnosed T1D, indicating that beta cell activity was preserved (ClinicalTrials.gov identifier: NCT00730392).

### Table 2 Immune Interventions in T1D

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Immune Target</th>
<th>Immunotherapy Clinical Trial Study</th>
<th>References</th>
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<tbody>
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In a double-blind, placebo-controlled clinical trial, non-diabetic children between the ages of 4 and 17.9 who had autoantibodies to glutamate decarboxylase (GADA), insulin, or zinc-transporter 8 were randomized, stratified by 2 or more islet autoantibodies, to 2 injections of 20 g GAD-Alum or placebo, spaced 30 days apart. In young children with prediabetes, GAD-Alum as a subcutaneous prime and boost injection was safe, but it had little impact on the development of T1D (ClinicalTrials.gov identifier: NCT01122446). In recent-onset T1D, a double-blind placebo-controlled intervention with glutamic acid decarboxylase (GAD)-alum, vitamin D, and Ibuprofen was conducted (T1D). 64 T1D patients were randomized (age 10–17.99 years, fasting c-peptide 0.12 nmol/l, GADA-positive). A linear relationship was found between baseline c-peptide, HbA1c, and insulin/per kilogram/24 h and change in c-peptide AUC after 15 months. c-peptide was not preserved by ibuprofen, vitamin D, or GAD-alum. Baseline clinical and immunological variables, as well as vitamin D levels, all affected treatment success (Clinical Trial Registration Identifier: NCT01785108).

In a multicenter phase 2 trial, randomly assigned, double-blind, placebo-controlled patients with newly diagnosed T1D aged between 18–45 years, positive for islet autoantibody, and with stimulated c-peptide of greater than 0.2 nmol L⁻¹ on a mixed meal tolerance test (MMTT) were included. At a dose of 400 mg imatinib mesylate (4X100 mg of film-coated tablets per day) is administered. A 26-week treatment of imatinib retained beta cell function at 12 months (ClinicalTrials.gov, Identifier: NCT01781975). Determining the appropriate dosage and duration of treatment, safety, and efficacy of imatinib in children, the use of complementary medications in combination, and imatinib’s ability to delay or arrest the progression of diabetes in a population at risk. A double-blind experiment comprised 87 newly diagnosed T1D patients aged 8 to 40 rituximab treatment decreased CD19+ B cells, lowered glycated hemoglobin levels, and needed less insulin. The use of rituximab preserved beta-cell activity (ClinicalTrials.gov identifier: NCT00279305). The discovery that B lymphocytes contribute to the pathophysiology of T1D may offer up a new avenue in the treatment of this ailment. In this two-year trial, participants are given one of three teplizumab infusion regimens (14-day full dosage, 14-day reduced dose, or 6-day full dose). Teplizumab immunotherapy inhibits deterioration in beta-cell function and improves glycemic control with reduced insulin dosages (ClinicalTrials.gov, Identifier NCT00385697).

The T1D TrialNet Study Group showed that low-dose anti-thymocyte globulin (ATG) (2.5 mg/kg) retained beta-cell function and lowered HbA1c for 1 year in new-onset T1D in a three-arm, randomized, double-masked, placebo-controlled phase 2b trial. 29 individuals received ATG plus pegylated granulocyte colony-stimulating factor (GCSF), while the other 29 received ATG only. Compared to placebo, low-dose ATG (2.5 mg/kg) results in improvements in immune cell subsets, a decrease in HbA1c, and long-term preservation of beta-cell function. While the advantages of low-dose ATG were diminished by the addition of GCSF (ClinicalTrials.gov Identifier: NCT02215200). Mycophenolate mofetil (MMF) alone or in combination with daclizumab (DZB) was evaluated in a multi-center, randomized, placebo-controlled, double-masked study to stop the loss of beta cells that produce insulin in newly diagnosed T1D (ClinicalTrials.gov Identifier: NCT00100178). Tocilizumab (IL-6R monoclonal antibody) was studied in a multicenter, randomized, placebo-controlled, double-blind experiment in people with newly diagnosed T1D. Immunophenotyping revealed decreases in IL-6R downstream signaling in T cells. However, there were no alterations in CD4 memory subsets, T helper 17 (Th17) cells, Tregs, or CD4+ T effector cell resistance to Treg suppression or prevent the rate of loss of residual beta cell function. During therapy, a dendritic cells (DC) subgroup declined, but when therapy ended, it returned to baseline (ClinicalTrials.gov Identifier: NCT02293837). Polyclonal Tregs and low-dose IL-2 were combined in a Phase I study (TILT trial), to improve Treg survival and expansion. Patients with T1D received a single infusion of autologous polyclonal Tregs, then one or two 5-day doses of human low-dose IL-2 (Id-IL-2). Therapy increased the amount of endogenous and infused Tregs, but it also increased the number of activated NK, mucosal-related invariant T, and clonal CD8+ T cells (ClinicalTrials.gov Identifier: NCT02772679). These findings have significant ramifications for the use of Id-IL-2 and Tregs in the treatment of autoimmune diseases in patients who already have active immunity. The safety and efficacy of a multi-dose Bacillus Calmette-Guérin (BCG) vaccination for the prevention of infectious illness in T1D in randomised, double-blind, placebo-controlled phase 2/3 trial was studied (ClinicalTrials.gov Identifier: NCT02081326). To modify autoimmune illnesses in an antigen-specific manner and to interfere in the pathophysiology of T1D, tolerogenic dendritic cells (tolDCs) are thought to be an appealing strategy. In T1D, C19-A3, a naturally produced proinsulin peptide, demonstrates activated immunological responses, and tolDCs that present this peptide can induce proinsulin-specific regulatory T cells.
Administration of autologous tolDCs pulsed with proinsulin peptide intra-dermally slow the gradual loss of beta-cell function with a shorter duration of T1D and retained c-peptide production.

**Therapy Approaches for Prevention of LADA**

The physician faces significant challenges in identifying and treating LADA. A consensus statement from a global expert panel discussed some key points for future action, such as a) screening for LADA, b) personalized medicine, c) the need for more randomized controlled comparative trials with hypoglycemic agents, d) further investigation of immune therapy, e) large-scale long-term studies in different patient populations, f) quality of life/lifestyle issues, g) studies including patients of different ethnic origin) the nature/quality of autoantibody assays.44

There are few clinical studies with LADA. Randomized, double-blind, placebo-controlled, dose-escalation clinical trial in a total of 47 LADA patients who received 4, 20, 100, or 500 Ag Diamyd subcutaneously at weeks 1 and 4. The ratio of CD4+ CD25+ to CD4+ CD25- cells rose. The stimulatory effects of 20 Ag Diamyd on both fasting and stimulated c-peptide were seen.98 In patients with LADA, strict glycemic management is the foundation for preventing or delaying beta-preserved cell loss and decreasing the onset of diabetes complications. Insulin, insulin sensitizers, sodium-glucose co-transporter 2 inhibitors, dipeptidyl peptidase-4 inhibitors, and receptor agonists are all used to treat LADA.70 In preliminary research, rosiglitazone, and insulin may help LADA patients maintain islet beta cell activity.99

A double-blind, randomized, controlled trial demonstrated that linagliptin medication reduces the rate of fall in C-peptide levels by raising endogenous glucagon-like Peptide 1 (GLP-1) levels to protect beta cells in LADA patients during a two-year follow-up.100 Recent data suggest that adding 2000 IU of vitamin D3 per day to the dipeptidyl peptidase-4 inhibitor saxagliptin may preserve beta cell function in LADA patients.101

**Conclusion**

Immunotherapies have shown promise in targeting the immune system, but they have not yet been able to achieve long-term glycemic control or preserve insulin secretion in people with type 1 diabetes (T1D) or latent autoimmune diabetes in adults (LADA). This is because the autoimmune destruction of beta cells in these conditions is often severe, and immunotherapies alone cannot reverse the damage. However, they may be able to slow the rate of beta cell loss, and the duration of glycemic control may be extended through the refinement of various immunotherapies. Single-target immunotherapies have not yet been able to fully restore T1D or LADA. However, progressive research in a clinical context should focus on improving intervention doses, doing more thorough examinations of intervention responders, and/or combining minimally effective single-target immunotherapies. This may lead to the development of more effective and durable immunotherapies for T1D and LADA.

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