Hormone Research in Paediatrics

Review Article

Horm Res Paediatr 2023;96:631–645
DOI: 10.1159/000524866

Received: December 14, 2021
Accepted: April 18, 2022
Published online: May 9, 2022

Recent Advances in Immune-Based Therapies for Type 1 Diabetes

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Keywords
Type 1 diabetes · Immunotherapy · Clinical trials · Prevention · Beta-cell preservation

Abstract
Background: Type 1 diabetes (T1D) is a chronic autoimmune disease characterized by progressive destruction of the pancreatic beta cells, leading to a lifelong dependence on insulin. It is associated with an increased morbidity and mortality from diabetes-related complications and a significant treatment burden. However, there has been substantial progress in therapeutic strategies that can affect the course of the disease. ***Summary:*** This review addresses advances in immunotherapy aimed at preserving residual beta-cell function in individuals with a recent onset of T1D and arresting the disease in pre-symptomatic stages. Recent and ongoing clinical trials have investigated the efficacy and safety of various immunotherapeutic strategies aimed at targeting several mechanisms of autoimmunity, which are thought to be important in disease pathogenesis, and therapies that also address beta-cell health. So far, T-cell-directed therapies that led to a favourable balance between T-effector cell depletion or modulation and preservation or expansion of regulatory T cells have shown the most success. Furthermore, regarding the timing of intervention, teplizumab was the first immunomodulatory agent to demonstrate a significant delay in disease progression in high-risk individuals before clinical onset. ***Key Messages:*** As more targeted immune interventions with potentially fewer side effects are closer to the translation into clinical practice, some new challenges may need to be addressed. The use of combination approaches that include immunotherapeutic strategies targeting different aspects of the immune system and interventions that improve beta-cell health may be required, along with the use of individualized patient-tailored approaches, a move towards early intervention, and a focus on patient-reported outcome measures.
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Introduction

Type 1 diabetes (T1D) is an autoimmune disease characterized by the destruction of the insulin-secreting beta cells, leading to insulin deficiency requiring lifelong treatment with exogenous insulin for survival. The disease affects 1.1 million children and adolescents worldwide and represents one of childhood's most prevalent chronic diseases. About 98,200 children under the age of 15 years develop the disease each year globally, and for reasons that are not understood, the incidence of T1D has been increasing, especially in young children [1]. Despite significant advances in diabetes management by introduc-

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ing faster acting insulin analogues, glucose-sensing devices, insulin pumps, and hybrid closed-loop pump-sensor systems, only a minority of people with T1D, especially adolescents and young adults, meet recommended glycaemic targets [2, 3]. Moreover, even with tight glycaemic control, T1D is linked to worse cardiovascular outcomes than the general population [4].

The aetiology of T1D is believed to be multifactorial and has not been fully elucidated. Human leucocyte antigen (HLA) genes have been identified as crucial genetic risk factors accounting for up to 50% of the genetic risk for T1D. Shared susceptibility genes in the HLA region contribute to the co-occurrence of other autoimmune diseases such as celiac disease [5]. Yet unknown trigger activates autoimmune response against beta cells [6, 7]. The immune response mainly involves an autoreactive effector CD4 and cytotoxic CD8 T lymphocytes [8]. Beta cells are likely attacked directly by cytotoxic T lymphocyte-mediated lysis and the secretion of pro-inflammatory cytokines, which recruit and activate additional inflammatory cells. Insulitis has been demonstrated by CD8 and CD4 T lymphocytes, macrophages, and B lymphocytes in human pancreatic islets [9]. In addition, deficits in peripheral tolerance, which have an essential role in restraining self-reactive T cells, may be significant in disease development [10, 11]. The initial laboratory manifestation of an autoimmune response against beta cells is the appearance of T1D-related autoantibodies, which are thought to be a marker rather than a mediator of beta-cell autoimmunity. Several antibodies against beta-cell components have been identified: insulin autoantibodies, antibodies to glutamic acid decarboxylase (GAD), antibodies to an aborted tyrosine phosphatase, which has been called islet antibody-2, and antibodies to the zinc transporter [12]. Seroconversion is an important preclinical marker of the T1D process. Longitudinal studies have shown that 95% of patients who progress to symptomatic T1D are autoantibody positive by 5 years of age [13]. If two or more antibodies appear, there is a significant chance of developing diabetes over the next two decades [14]. Thus, according to the new classification, the presence of two or more different antibodies defines the first stage of T1D. The second stage is characterized by progressive metabolic changes such as losing the first-phase insulin response during the intravenous glucose tolerance test, followed by dysglycaemia. The third stage occurs when T1D is diagnosed, which is most likely when clinical symptoms of diabetes become apparent. Approximately half of the beta cells have lost function at this stage; however, further progressive decline of beta-cell function follows [15].

There is increasing recognition that T1D is a heterogeneous disease with regard to the clinical factors such as wide age range at onset, rate of disease progression, level of glycaemic control, variable insulin requirements, and susceptibility to acute and chronic complications as well as pathobiological mechanisms such as underlying genetic predisposition, islet autoantibody patterns, and histology of pancreatic tissue. Based on these factors, distinct T1D subtypes called endotypes can be defined [16]. Birth cohort studies of subjects with a high risk of T1D have identified two major patterns of appearance of the first islet autoantibody as a marker of islet autoimmunity. Insulin antibodies-initiated islet autoimmunity has early peak of incidence before 2 years of age and is strongly linked to the HLA-DR4 haplotype. On the other hand, GAD autoantibodies emerge as the first marker of autoimmunity later and are strongly correlated to the HLA-DR3 haplotype [17, 18]. Furthermore, two distinct types of insulitis were present in subjects with recent-onset T1D. Younger subjects (<7 years of age) at diabetes onset had a higher proportion of CD20+ B cells. On the other hand, CD20+ B cells were almost absent in those with diabetes diagnosed beyond the age of 13 years. Likewise, those who received a diagnosis in their early years had a much lower proportion of insulin-containing islets left than those with an older age at onset, implying differently aggressive autoimmune response. Furthermore, proinsulin processing was aberrant to a much greater degree among children with recent-onset T1D diagnosed before age 7 years than among those diagnosed at age 13 years or older [19, 20].

Based on these findings, immunotherapeutic approaches to modify the course of T1D have been developed. Intervention before any evidence of autoimmunity is called primary prevention. Secondary prevention occurs after the development of diabetes-related autoantibodies but before the onset of hyperglycaemia [21]. Such interventions aim at arresting the immune process and, thus, prevent or delay clinical disease. At the time of diagnosis, which indicates the third stage, residual beta cells are present. At this stage, suppression of beta-cell autoimmunity would protect the remaining beta-cell mass [22]. As tight glycaemic control is needed to mitigate diabetic complications, the maintenance of beta-cell function could help in the management of hyperglycaemia as well as reduce the resultant complications [23]. Recent advances have made available targeted therapy for defined immune response pathways (shown in Fig. 1). Administration of immunosuppressive drugs in new-onset T1D has delayed or stopped diabetes progression. However,

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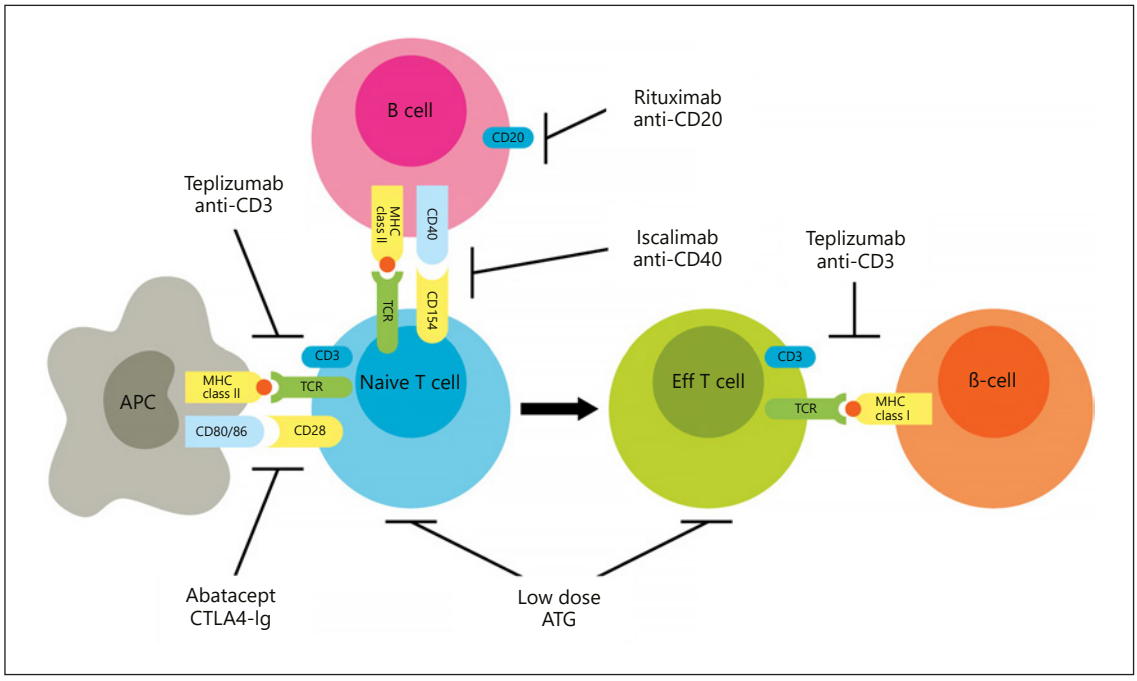

Fig. 1. Summarized targets for immune intervention in T1D. APC, antigen-presenting cell; Eff T cell, effector T cell; TCR, T-cell receptor; ATG, anti-thymocyte globulin; CTLA4-Ig, cytotoxic T lymphocyte-associated protein 4; MHC, major histocompatibility complex.

loss of beta-cell function resumed after the treatment was withdrawn [24]. In individuals with established T1D with little remaining beta cells, transplantation of allogeneic beta cells or generated autologous beta cells may require an immune intervention that halts the autoimmune attack [25]. To accelerate the delivery of new immunotherapies to clinical use in people with T1D, international networks between clinical investigators and scientists such as the Type 1 Diabetes TrialNet [26] and the INNODIA (translational approaches to disease-modifying therapy of type 1 diabetes: an innovative approach towards understanding and arresting type 1 diabetes) [27] have been established. This review highlights recent landmark and ongoing clinical trials related to immune interventions for T1D, their respective outcomes, and future directions (Table 1).

T-Effector Lymphocyte-Based Therapy

Low-Dose Anti-Thymocyte Globulin

Anti-thymocyte globulin (ATG) is a pasteurized solution primarily of rabbit-derived polyclonal immunoglobulin G (IgG) antibodies directed against multiple T-cell antigens [28]. ATG is a potent immunosuppressant and immunomodulator, but it is not fully understood which specificities mediate the alteration in immunoregulation. A drop in the number of circulating T cells probably constitutes the primary mechanism of immunosuppression. In addition, changes in lymphocyte subsets, including reversal of the CD4/CD8 ratio, have been observed (shown in Fig. 1) [29]. ATG has been used for many years as an immunosuppressive agent for organ transplantation and treatment of aplastic anaemia [30, 31]. As T1D is thought to be a T-cell-mediated disease, ATG could preserve beta-cell function through the ability to target multiple T-cell pathways. The efficacy of ATG in T1D has been previously reported in clinical studies where different doses were assessed and where ATG was used as monotherapy as well as in combination therapy [32–34].

In the Study of Thymoglobulin to ARrest T1D (START), high-dose ATG treatment (6.5 mg/kg) for 4 days in participants with new-onset T1D, aged 12–35 years, failed to achieve preservation of beta-cell function 12 months later. Generalized T-cell depletion in the absence of specific depletion of effector memory T cells and preservation of regulatory T cells (Tregs) seemed to be an ineffective treatment for T1D [32]. In post hoc analyses, ATG preserved C-peptide secretion 24 months later in older (age 22–35 years) participants but did not pre-

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Table 1. Overview of recent immune intervention trials in T1D

Study/ID/phase/status	Intervention	Dose/route of administration	Enrolment/age range/T1D stage	Primary outcome
ATG-G-CSF in New Onset Type 1 Diabetes/ NCT02215200/phase 2/completed [34]	ATG G-CSF	2.5 mg/kg as two divided IV infusions in 2 consecutive days 6 mg SC every 2 weeks for a total of 6 doses	89/12–45 years/new-onset T1D (stage 3)[1]	AUC of stimulated C-peptide response over the first 2 h of a 4-h MMTT conducted at the 12-month visit
Phase II, Dose Ranging, Efficacy Study of Anti-thymocyte Globulin (ATG) Within 6 Weeks of Diagnosis of Type 1 Diabetes (T1D) (Meld-ATG)/ NCT04509791/phase 2/ongoing	ATG	2.5 mg/kg or lower dose as two divided IV infusions in 2 consecutive days	114/5–25 years/new-onset T1D (stage 3)[1]	AUC of stimulated C-peptide response over the first 2 h of a MMTT at 12 months post-treatment
Teplizumab for Prevention of Type 1 Diabetes In Relatives "At-Risk"/NCT01030861/phase 2/completed [50]	Teplizumab	IV infusions given for 14 consecutive days with escalating doses, each infusion takes about 30 min	76/8–45 years/relatives at very high risk for developing disease (stage 2)[1]	Rate of new diabetes per year during median follow-up of 745 days
Recent-Onset Type 1 Diabetes Trial Evaluating Efficacy and Safety of Teplizumab (PROTECT)/ NCT03875729/phase 3/ongoing	Teplizumab	Two courses 6 months apart; each course of treatment will include IV infusions given for 12 consecutive days	300/8–17 years/new-onset T1D (stage 3)[1]	The AUC of C-peptide after a MMTT at week 78
CTLA4-Ig (Abatacept) for Prevention of Abnormal Glucose Tolerance and Diabetes in Relatives At-Risk for Type 1/NCT01773707/phase 2/ongoing	CTLA4-Ig (abatacept)	14 (30 min) infusions over 1 year (3 infusions every other week the first month; monthly for the following 11 months)	212/6–45 years/at-risk autoantibody-positive non-diabetic relatives of patients with T1D (stage 1)[1]	Change from normal glucose tolerance to abnormal glucose tolerance every 6 months for 5–6 years
Study of Safety and Efficacy of CFZ533 in Type 1 Diabetes Pediatric and Young Adult Subjects (CCFZ533X2207)/NCT04129528/phase 2/ongoing	CFZ533 (iscalimab)	First dose is administered via IV infusion, subsequent doses are administered SC	102/6–21 years/new-onset T1D (stage 3)[1]	To evaluate safety and tolerability of CFZ533 in new-onset T1D Stimulated C-peptide AUC by MMTT at 12 months
Safety and Efficacy of CLBS03 in Adolescents With Recent Onset Type 1 Diabetes (The Sanford Project T-Rex Study)/NCT02691247/phase 2/completed	CLBS03 (autologous ex vivo expanded polyclonal regulatory T-cells)	A single infusion of CLBS03 (high- or low-dose)	113/8–17 years/new-onset T1D (stage 3)[1]	Stimulated C-peptide AUC by 4-h MMTT at 52 weeks
Dose Finding Study of Il-2 at Ultra-low Dose in Children With Recently Diagnosed Type 1 Diabetes (DFIL2-Child/NCT01862120/phase 1/2/completed [89]	Human recombinant interleukin-2 (rhIL-2)	Induction period: subcutaneous injection of IL-2 during 5 days, once daily Maintenance period: at day 15, single administration of IL-2 every 2 weeks during 1 year	24/7–14 years/new-onset T1D (stage 3)[1]	Treg response following the induction cure period at day 5 expressed as % total CD4 cells
A Study of SIMPONI® to Arrest Beta-cell Loss in Type 1 Diabetes (T1GER)/NCT02846545/phase 2/completed [96]	Golimumab	Induction dose of subcutaneous golimumab at weeks 0 and 2, followed by maintenance subcutaneous doses at week 4 and every 2 weeks through week 52	84/6–21 years/new-onset T1D (stage 3)[1]	Stimulated C-peptide AUC by 4-h MMTT at week 52
A Clinical Proof-of-principle Trial in Adult Subjects With Newly Diagnosed Type 1 Diabetes Mellitus Investigating the Effect of NNC0114-0006 and Liraglutide on Preservation of Beta-cell Function/ NCT02443155/phase 2/completed [100]	NNC0114-0006 (monoclonal anti-IL-21 antibody) Liraglutide	NNC0114-0006 12 mg/kg administered IV every 6 weeks, for 54 weeks Liraglutide 1.8 mg administered SC daily, for 54 weeks	308/18–45 years/new-onset T1D (stage 3)[1]	Stimulated C-peptide AUC by 4-h MMTT at week 54
Imatinib Treatment in Recent Onset Type 1 Diabetes Mellitus/NCT01781975/phase 2/completed [105]	Imatinib mesylate	400 mg imatinib mesylate (4 × 100 mg film-coated tablets) per day) for 26 weeks	67/18–45 years/new-onset T1D (stage 3)[1]	AUC of stimulated C-peptide response over the first 2 h of a 4-h MMTT conducted at the 1-year visit
Pre-POINT-Early Study/NCT02547519/phase 1/2/ completed [110]	Oral insulin	Daily treatment with dose escalation scheme, total of 12 months treatment	44/6 months–2.99 years/first-degree relatives of people with T1D and have a susceptible HLA genotype, islet autoantibody negative at time of recruitment (pre-stage 1)[1]	The activation of a CD4+ T-cell immune response against insulin at 12 months of treatment
GAD-Alum (Diamyd) Administered Into Lymph Nodes in Combination With Vitamin D in Type 1 Diabetes/ NCT03345004/phase 2b/completed [112]	GAD-alum (Diamyd®)	Three intra-lymphatic injections with Diamyd on three occasions and oral vitamin D 2,000 IU/daily for 4 months	109/12–24 years/new-onset T1D (stage 3)[1]	Change in stimulated C-peptide AUC during 2 h MMTT between baseline to 15 months

T1D, type 1 diabetes; ATG, anti-thymocyte globulin; G-CSF, granulocyte colony-stimulating factor; IV, intravenous; SC, subcutaneously; AUC, area under the curve; MMTT, mixed-meal tolerance test; CTLA4-Ig, cytotoxic T-lymphocyte-associated protein 4; IL-2, interleukin-2; IL-21, interleukin-21; HLA, human leucocyte antigen; GAD, glutamic acid decarboxylase. [1]Stages of type 1 diabetes: pre-stage 1 (genetic susceptibility), stage 1 (autoimmunity/normoglycaemia/pre-symptomatic type 1 diabetes), stage 2 (autoimmunity/dysglycaemia/pre-symptomatic type 1 diabetes), stage 3 (symptomatic type 1 diabetes) [15].

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serve islet function in most individuals with new-onset T1D [35].

In a pilot study by Haller et al. [33], lower dose of ATG (2.5 mg/kg) was used along with granulocyte colony-stimulating factor (G-CSF) in individuals with established T1D (T1D duration 4–24 months), aged 12–45 years. At 12 months post-therapy, the mean area under the curve (AUC) C-peptide was significantly higher in the treated compared to the placebo group ($p = 0.017$). Less severe T-cell depletion compared to a high dose and significantly higher number of Tregs were also observed [33]. At 24 months, mixed-meal tolerance test (MMTT)-stimulated AUC C-peptide remained greater in ATG + G-CSF-treated patients (0.49 nmol/L/min) compared with placebo (0.29 nmol/L/min), but the difference was not significant [36]. After 5 years, there were no statistically significant differences in AUC C-peptide when comparing those who received ATG/G-CSF versus placebo [37]. In a phase 2b clinical study, 89 subjects with newly diagnosed T1D (<3 months post-diagnosis), aged 12–45 years were divided into three groups and received a low-dose ATG alone (2.5 mg/kg), a combination of low-dose ATG with G-CSF (36 mg) or placebo. Low-dose ATG resulted in a significantly higher mean AUC C-peptide and glycated haemoglobin A1c (HbA1c) improvement at 12 months. The addition of G-CSF did not result in a further increase of C-peptide levels over low-dose ATG monotherapy [34]. Two-year clinical trial outcome data confirmed a sustained effect of low-dose ATG on C-peptide [38]. Thus, low-dose ATG has demonstrated considerable long-term capacity to preserve beta-cell function. As reported by Haller et al. [34], no potential safety signals were seen in low-dose ATG-treated new-onset T1D subjects. Only short-lived and fully reversible side effects such as cytokine release syndrome (CRS) and serum sickness were reported in the study group. Serum sickness was observed in the majority of participants who received low-dose ATG, but this was predictable and manageable. In addition, none of the participants who received low-dose ATG developed a severe infection, required extended hospitalization or readmission due to CRS or serum sickness, and no cases of grade 4 serum sickness or CRS were reported [34].

Since previous studies demonstrated the efficacy of ATG in C-peptide preservation with an acceptable safety profile, a phase 2, multicentre, randomized, double-blind, placebo-controlled, multi-arm parallel cohort trial of ATG in new-onset T1D (<9 weeks post-diagnosis) 5- to 25-year-old subjects is currently being conducted by INNODIA. The study aims to determine whether the 2.5 mg/kg ATG dose is superior to placebo, search for a minimally effective dose, and assess the safety profile of different doses of ATG in different age groups (NCT04509791) [39]. Moving forward, TrialNet will test low-dose ATG in the T1D prevention study (NCT04291703) [40].

Anti-CD3 Antibodies

CD3 acts as a T-cell co-receptor involved in the activation and differentiation of both CD8 and CD4 naive T-cells. Anti-CD3 monoclonal antibodies block the union of CD3 with T-cell receptor and subsequently prevent the activation of T cells, especially CD8+ T lymphocytes, involved in beta-cell destruction [41] (shown in Fig. 1). In addition, anti-CD3 monoclonal antibodies increase CD4+ Tregs, thus promoting self-tolerance [42]. Anti-CD3 immunological pathway has been extensively studied in T1D. Furthermore, after humanized anti-CD3 antibodies with reduced binding to the low-affinity IgG Fc receptors were developed [43], several studies with teplizumab, an Fc receptor non-binding humanized anti-CD3 monoclonal antibody, have documented the decreased loss in C-peptide levels in recent-onset T1D [44–46]. The phase II Autoimmunity-Blocking Antibody for Tolerance in Recently Diagnosed Type 1 Diabetes (AbATE) trial of teplizumab was a randomized, open-label study in new-onset T1D subjects (8–30 years old, T1D duration ≤8 weeks). The treatment group received teplizumab at a cumulative median dose of 11.6 mg over 14 days. The subjects, which had detectable C-peptide levels, received a second course of the drug at 12 months. At 24 months, the adjusted mean C-peptide AUC level at year 2 was 75% higher in the treatment group compared to controls. However, there was no significant difference in HbA1c between the groups during the entire study. An important finding was that a subgroup of responders, defined as those in the treatment group with <40% of C-peptide loss from enrolment, had lower HbA1c and daily insulin requirements at baseline and subtly increased circulating CD8+ central memory T-cells. On the other hand, the non-responders were almost indistinguishable from the controls [47]. Fifty-six percent of the original participants with detectable C-peptide at year 2 of AbATE returned for follow-up. C-peptide responses were assessed by a 4-h mixed-meal tolerance test. Overall, the C-peptide responses were not significantly different at the follow-up visit when comparing the drug-treated and control groups. However, the drug-treated responders presented reduced declines in the loss of beta-cell function, as assessed by C-peptide loss, even after 7 years from diagnosis. The improve-

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ments in C-peptide response were not associated with lower HbA1c levels or insulin use. Due to the greater frequency of programmed cell death protein 1 expression on central memory CD8+ T cells in the drug-treated responders, there was a significantly increased frequency of programmed cell death protein 1-positive central memory and anergic CD8+ T-cells at follow-up in drug-treated responders compared to the non-responders or the control individuals [48].

The TrialNet anti-CD3 prevention trial with teplizumab enrolled 76 pre-symptomatic relatives (at least 8 years of age, 72% were ≤18 years of age). The participants had at least two or more pancreatic islet autoantibodies and dysglycaemia on an oral glucose tolerance test (stage 2 T1D), thus having a very high risk of progressing to T1D within a few years and the lifetime risk of insulin-dependent clinical disease (stage 3 T1D) approaching 100% [49]. Teplizumab was administered over 14 days in the outpatient setting with escalating doses to decrease adverse events related to cytokine release. The primary endpoint was the elapsed time from randomization to the clinical diagnosis of diabetes. T1D was diagnosed in 19 (43%) in teplizumab and 23 (72%) in placebo groups. The annualized rates of diagnosis of T1D were 14.9% per year in the teplizumab group and 35.9% per year in the placebo group. The median time to diabetes diagnosis was 48.4 months in the teplizumab group and 24.4 months in the placebo group (hazard ratio, 0.41, $p = 0.006$). The treatment was well-tolerated, with the expected transient adverse events of rash and lymphopaenia being the most common. In the subgroup analysis, the greater likelihood of response was observed with the absence of HLA-DR3, presence of HLA-DR4 and in individuals without anti-zinc transporter 8 antibodies [50].

In the updated analysis over a median follow-up of 923 days, the effect of teplizumab was sustained. The median time to diabetes was 59.6 months in the intervention group and 27.1 months in the placebo group. Thus, the onset of clinical disease and insulin dependence was delayed by approximately 3 years (median of 32.5 months). In addition, 50% of those treated with teplizumab remain diabetes-free, compared to only 22% of those taking placebo. The hazard ratio for the development of T1D in teplizumab-treated participants versus placebo was 0.457 ($p = 0.01$). The longest follow-up free of diabetes in the teplizumab group was more than 8 years. Treatment with teplizumab was also reported to reverse the decline in C-peptide levels (C-peptide AUC 1.94 vs. 1.72 pmol/mL; $p = 0.006$). The changes in C-peptide were associated with increases in partially exhausted CD8+ T cells that showed reduced secretion of interferon gamma (IFNg) and tumour necrosis factor alpha (TNFa) [51].

A phase 3, randomized, double-blind, placebo-controlled, multinational, multicentre Recent-Onset Type 1 Diabetes Trial Evaluating Efficacy and Safety of Teplizumab (PROTECT) trial involving children and adolescents 8–17 years old recently diagnosed with T1D is ongoing. Subjects will receive two courses of either teplizumab or placebo treatment 6 months apart. Each course of treatment will include daily infusions for 12 days. The primary objective is to determine whether two courses of teplizumab administered 6 months apart decelerate the loss of beta cells and preserve beta-cell function over 18 months. The secondary objectives are to evaluate improvements in key clinical parameters of diabetes management, determine the safety and tolerability, and evaluate the pharmacokinetics and immunogenicity of teplizumab (NCT03875729) [52]. In addition, pharmacokinetic/pharmacodynamic data will help determining comparability between the commercial drug product and the drug product manufactured for historical trials of teplizumab and potentially help in the process of the US Food and Drug Administration (FDA) approval of teplizumab in at-risk individuals.

Otelixizumab was another humanized anti-CD3 monoclonal antibody with a similar reduction in T-cell activation. In a randomized, placebo-controlled, phase 2 study, otelixizumab (48–64 mg) was administered over 6 days to 40 individuals with new-onset T1D (12–39 years). At 6, 12, and 18 months of follow-up, subjects in the treatment group had partially preserved beta-cell function with lower insulin requirements compared to the control group. No significant differences were observed in the HbA1c level [53]. After 4 years of follow-up, the otelixizumab group had lower insulin requirements despite similar HbA1c [54]. Transient Epstein-Barr virus (EBV) reactivation was seen in more than 75% of the treatment group [53]. Two follow-up phase 3, industry-sponsored, randomized controlled trials, Durable Response Therapy Evaluation for Early or New-Onset Type 1 Diabetes (DEFEND)-1 and -2, enrolled new-onset T1D participants 12–45 years old. To reduce rates of EBV reactivation lower dose of otelixizumab (3.1 mg) was used. Although eliminating EBV reactivation and CRS, these studies failed to meet their primary endpoints, the change in C-peptide levels at 12 months [55, 56]. Subcutaneous otelixizumab was associated with injection site adverse effects, which were dose-dependent and lasted up to 2 weeks in some cases [57].

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Co-Stimulation Modulators

T cells require T-cell receptor interaction with peptides presented by antigen-presenting cells (APCs) and co-stimulatory signals to become fully activated. The cytotoxic T lymphocyte-associated protein 4 (CTLA4-Ig), also known as abatacept, comprises a human CTLA4 receptor fused to a modified Fc portion of human IgG. As a homologue of CD28, it inhibits CD28-mediated T-cell co-stimulation by binding to CD80/CD86 on APCs, preventing ligation of CD28, which interferes with T lymphocyte activation, proliferation, and differentiation (shown in Fig. 1). Abatacept is a component of therapies in several human autoimmune diseases, especially rheumatoid arthritis [58, 59]. TrialNet evaluated abatacept therapy in 112 subjects with new-onset T1D (6–45 years old, T1D duration <100 days) randomized in a 2:1 design. The treatment group received monthly infusions of abatacept over 2 years. At the end of the treatment period, the abatacept group had a 59% higher adjusted C-peptide AUC compared to placebo ($p = 0.0029$). However, a progressive decline of C-peptide AUC in the abatacept group parallelling the placebo group was observed after 6 months of treatment. Nevertheless, treatment was well-tolerated with mild adverse events, such as headache, nausea, and diarrhoea [60]. Immunological studies showed that the expansion of naive CD4 T-cells was associated with a significantly slower rate of C-peptide decline in the abatacept group. There was also a significant reduction from baseline at 6, 12, and 24 months in the median percentage of Tregs, which had returned to the baseline at 30 months. In the placebo group, an increase in central memory CD4 T-cells during a preceding visit was significantly associated with C-peptide decline at the subsequent visit [61]. After therapy was stopped, subjects were followed for an additional year, with MMTTs performed at 30 and 36 months. At 36 months, the abatacept group maintained a difference in C-peptide AUC from the placebo group ($p = 0.046$). A progressive parallel rate of C-peptide decline was observed in both groups but with an estimated 9.5 months delay with abatacept. In addition, HbA1c levels remained lower in the abatacept group than in the placebo group. Still, the mean total insulin dose among the abatacept group was the same as the placebo group [62]. The study by Cabrera et al. [63] aimed to determine whether discrete subtypes of T1D exist based on immunoregulatory profiles at clinical onset of CTLA4-Ig trial participants. As a result, four age-independent subgroups were identified that differed in terms of baseline innate inflammatory/regulatory bias, rate of C-peptide decline, and response to CTLA4-Ig treatment [63]. Ongoing TrialNet clinical trial (NCT01773707) will analyse the benefits of abatacept in delaying progression from stage 1 to stage 2 or 3 T1D in autoantibody-positive relatives of individuals with clinically overt T1D, aged 6–45 years old [64].

Alefacept is another T-cell co-stimulation blocking agent. The anti-CD2 fusion protein binds to CD2 on CD4+, and CD8+ T lymphocytes inhibits their activation and induces apoptosis of memory T lymphocytes. Earlier studies in psoriasis had demonstrated that alefacept selectively targets effector memory T cells [65]. In the Inducing Remission in New-Onset Type 1 Diabetes with Alefacept (T1DAL) trial, 49 subjects aged 12–35 years, with recent-onset stage 3 T1D (<100 days) were randomized in a 2:1 design. Alefacept or placebo was administered as two 12-week courses of monthly intramuscular injections. At 12 months, C-peptide during the 4 h of the MMTT indicated a significant difference in beta-cell function. Still, C-peptide during only the first 2 h of the MMTT did not reach statistical significance. The mechanistic evaluation revealed that alefacept significantly reduced CD4 and CD8 effector and memory cells, with more remarkable preservation of Tregs, leading to a favourable Treg: Teff ratio [66]. At 24 months, the 4-h and the 2-h C-peptide levels were greater in the alefacept group than in the placebo group. A substantial reduction in insulin dose and reduction of hypoglycaemic events by 50% was observed in alefacept-treated individuals [67].

B-Lymphocyte-Based Targets

B Lymphocyte Depleting Therapy

Although T1D is considered an autoimmune T-cell-mediated disease, B cells are also implicated in its pathogenesis. The activated autoreactive B lymphocytes infiltrate the islets and increase as insulitis becomes more aggressive [9]. In addition, B-cells also act as APC populations for T-CD4+ cells [68]. Rituximab is a monoclonal antibody specific to B-cell surface protein CD20, required for B-cell activation and proliferation. Thus, rituximab substantially depletes B cells (shown in Fig. 1). The drug is used to treat B cell lymphomas and autoimmune diseases such as rheumatoid arthritis [69]. In a double-blind phase 2 study, 87 subjects aged 8–40 years diagnosed with T1D within the past 100 days were randomized in a 2:1 design to receive either four weekly doses of rituximab or placebo. At year one, the rituximab group had a higher mean

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AUC C-peptide (p = 0.03) but lower than baseline. The treatment group also had lower insulin requirements and lower HbA1c. However, after 30 months, the rate of decline of C-peptide showed no difference between the treatment group and placebo [70, 71]. Rituximab caused significant B-cell depletion, but the effect on beta-cell autoantibody titres was minimal, suggesting a beneficial but temporary effect of B-lymphocyte depletion due to impaired cross-talk between B and T cells [72]. RNA sequencing analysis of whole-blood samples revealed a transient increase in activity of T-cells, which was associated with more rapid C-peptide loss. Since combination treatment of rituximab followed by therapy targeting CD4 T-cells may be beneficial [73], TrialNet prevention study seeks to utilize sequential treatment with rituximab followed by abatacept (NCT03929601) in individuals with stage 2 T1D [74].

B Lymphocyte Non-Depleting Therapy

CD40 receptor is on APCs, such as B lymphocytes. Its ligand CD154 is transiently expressed on activated T cells. The CD40-CD154 interaction between B and T lymphocytes initiates a co-stimulatory pathway leading to T-cell-dependent humoral immune response and is essential for priming and activating CD4+ autoreactive T lymphocytes and CD8+ cytolytic T lymphocytes [75, 76]. Iscalimab (CFZ533) is a fully human, anti-CD40 monoclonal antibody that targets the CD40-CD154 co-stimulatory pathway (shown in Fig. 1), resulting in the B-cell activation signal's attenuation without depleting peripheral blood B cells (Fc-silent). In vitro, iscalimab inhibits CD154-induced activation on multiple cell types, including B lymphocytes, macrophages, and epithelial cells. In addition, in non-human primates, iscalimab blocked primary and recall T-cell-dependent antibody responses and suppressed germinal centre formation [77]. Iscalimab is in clinical development for several autoimmune conditions such as Sjogren's syndrome [78] and Graves' disease [79]. The CD40-CD154 pathway is hypothesized to play an important role in the pathogenesis of T1D by priming autoreactive T cells via activated diabetogenic B lymphocytes [80]. This is supported by clinical data in patients with T1D [81]. These data collectively suggest that blockade of CD40-CD154 interaction with iscalimab in individuals with new-onset T1D could provide a novel therapeutic approach for preserving residual beta-cell function. An ongoing phase 2, multicentre, non-confirmatory, investigator- and subject-masked, randomized, placebo-controlled study will evaluate the safety, tolerability, pharmacokinetics, and efficacy of CFZ533 on preserving residual pancreatic beta-cell function in new-onset T1D in paediatric and young adult subjects (NCT04129528) [82].

T Regulatory Cell-Based Therapy

Tregs are a subset of CD4+ T cells, which have an essential role in induction and maintenance of peripheral tolerance and are critical for preventing excessive immune responses and autoimmunity. Activation or delivery of Tregs has emerged as a potential tool for treating autoimmune diseases [83]. Non-randomized phase 1 trial showed that expansion and reinjection of large amounts of polyclonal Tregs are safe and tolerable in children with recent-onset T1D and might be able to maintain C-peptide production [84]. In an open-label, interventional phase 1 clinical trial, Tregs could be efficiently isolated from peripheral blood of fourteen adult subjects with recent-onset T1D and expanded within 2 weeks. Reinfusion of the Tregs had an excellent safety profile. However, infused Tregs in the peripheral blood dropped to 25% after 3 months. The study was not powered to detect the impact of Tregs on the beta-cell function [85]. To address this, a multicentre phase 2 randomized, placebo-controlled, double-blind clinical trial will determine the safety and effect on the beta-cell function of a single infusion of autologous ex vivo expanded polyclonal Tregs in 113 patients, aged 8–17 years, with recently onset T1D (NCT02691247) [86]. Ongoing phase 1/2 randomized, open-label study will evaluate the safety and therapeutic effect of infusion of ex vivo expanded umbilical cord blood Tregs and liraglutide therapy in adult individuals with autoimmune diabetes (NCT03011021) [87].

Interleukin-2 (IL-2) is an essential cytokine for Treg development and function. Treg cells constitutively express interleukin-2 receptor, unlike other T cells. IL-2, given at low doses, can selectively stimulate Tregs [88]. Various low doses of IL-2 for Tregs expansion and safety were examined in multicentre, double-blinded, placebo-controlled, dose-finding phase 1/2 study in children with recent-onset T1D. There were no serious adverse events. The most common non-serious adverse event was injection site reaction. After five daily injections, IL-2 induced a dose-dependent increase in the mean proportion of Tregs but with marked variation in response. Although the study was not powered to detect the impact on beta-cell function, high responders might have improved maintenance of induced C-peptide production at 1 year compared with low responders [89]. In the Interleukin-2

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Therapy of Autoimmunity in Diabetes (ITAD) phase II, multicentre, double-blind, randomized, placebo-controlled trial, 45 children and adolescents (6–18 years) will receive within 6 weeks of T1D diagnosis either ultra-low-dose IL-2 (aldesleukin) twice-weekly subcutaneously or placebo for 6 months. The primary objective is to assess the effects of ultra-low-dose aldesleukin administration on endogenous β-cell function measured by fasting and postprandial C-peptide with frequent home-dried blood spots (NCT03782636) [90]. Phase I T1D Immunotherapy Using Polyclonal Tregs + IL-2 (TILT) trial combined a single infusion of autologous expanded polyclonal Tregs and low-dose IL-2 in individuals with recent-onset T1D. Combination therapy led to an increase in the number of infused and endogenous Tregs but also resulted in a substantial increase of cytotoxic T cells [91].

Cytokine-Directed Therapy

Inflammation and pro-inflammatory cytokines are involved in the pathogenesis of T1D. Therapeutic inhibition of pro-inflammatory cytokines has been successfully used to treat other autoimmune diseases [92, 93]. Tumour necrosis factor α (TNF-α) plays an important role as an intermediary molecule in several autoimmune diseases [94]. In a small pilot phase 1/2 trial of etanercept (recombinant TNF-α receptor-IgG fusion protein) in children newly diagnosed with T1D (aged 7.8–18.2 years), treatment resulted in lower HbA1c and increased endogenous insulin production assessed by C-peptide levels. From baseline to week 24, the change in the C-peptide AUC showed a 39% increase in the etanercept group and a 20% decrease in the placebo group ($p < 0.05$), insulin dose decreased by 18% in the etanercept group compared with a 23% increase in the placebo group ($p < 0.05$), and HbA1c was lower in the etanercept group compared with that in the placebo group ($p < 0.05$) [95]. Another anti-TNF-α agent, golimumab (IgG1-κ monoclonal antibody), which is approved for the treatment of several autoimmune diseases, was tested in phase II, multicentre, placebo-controlled, double-blind, parallel-group trial (T1GER) [96]. Eighty-four participants (age range, 6–21 years) with newly diagnosed overt T1D receive subcutaneous golimumab or placebo for 52 weeks. Participants received an induction dose at weeks 0 and 2 according to their body surface area. Induction doses were followed by subcutaneous maintenance doses at week 4 and every 2 weeks through week 52. At week 52, the mean 4-h C-peptide AUC differed significantly between the golimumab and the placebo groups (0.64 pmol/mL vs. 0.43 pmol/mL, $p < 0.001$). Also, insulin use was lower with golimumab than with placebo, and a partial-remission response (defined as an insulin dose-adjusted glycated haemoglobin level score of ≤9) was observed in 43% of participants in the golimumab group and 7% in the placebo group (36 percentage points difference). There was no significant difference between the groups in HbA1c level and the mean number of hypoglycaemic events.

Combination Immunomodulatory and Beta-Cell Therapy

Interleukin-21 (IL-21) is overexpressed in pancreatic beta cells and leads to the secretion of inflammatory cytokines and chemokine, resulting in leukocytic infiltration and islet destruction in animal models. In humans, serum IL-21 and interleukin-17 (IL-17) are higher in T1D patients. Therefore, blocking IL-21 could enable beta-cell survival [97]. For anti-IL-21 antibody targeting IL-21, early clinical trials did not reflect significant safety risks or significant changes in laboratory safety parameters [98]. Glucagon-like peptide-1 receptor (GLP-1R) agonists liraglutide has been suggested to preserve functional beta cells by reducing metabolic stresses and preventing apoptosis [99]. Therefore, combined treatment could enable beta-cell survival with a reduced risk of complications compared with traditional immunomodulation. In a randomized, parallel-group, placebo-controlled, double-dummy, double-blind, phase 2 trial, 308 adults aged 18–45 years (an average of 28.4 years) with recently diagnosed T1D (≤20 weeks) and residual beta-cell function were randomly assigned (1:1:1:1) to receive 54 weeks of treatment with a combination of anti-IL-21 and liraglutide, anti-IL-21 alone, liraglutide alone, or placebo (77 assigned to each group). Anti-IL-21 was given intravenously at a dose of 12 mg/kg every 6 weeks, while 1.8 mg of liraglutide was self-administered once daily as subcutaneous injections. The change in MMTT-stimulated C-peptide concentration at week 54 (end of treatment) relative to baseline was measured via the AUC over 4 h. Compared to placebo (39% decrease), the decrease in MMTT-stimulated C-peptide concentration from baseline to week 54 (end of treatment) was significantly smaller with combination treatment (10% decrease; $p = 0.0017$) but not with anti-IL-21 or liraglutide alone. Despite greater insulin use in the placebo group, the reduction in HbA1c at week 54 was greater with all active treatments than with placebo, although the differences versus placebo were not

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significant. The trial included a 26-week observation period after treatment cessation at week 54. The benefits of treatment diminished rapidly upon treatment cessation. Adverse event profiles were consistent with previous reports on anti-IL-21 and the established safety profile of glucagon-like peptide-1 receptor agonists in type 2 diabetes. The most common adverse event was gastrointestinal disorders, a known side effect of liraglutide. Hypoglycaemic events occurred with a similar frequency in the treatment and the placebo groups, though the liraglutide group had a lower rate [100].

Tyrosine Kinase Inhibitors

Imatinib mesylate (Gleevec®) is a small-molecule multi-tyrosine kinase inhibitor approved for treatment of certain types of leukaemia, other cancers, and disorders of the blood cells. The drug treats cancer by inhibiting a small subset of tyrosine kinases, mediators of the signalling cascade involved in cell growth, proliferation, differentiation, metabolism, and apoptosis [101]. Case reports of cancer patients treated with tyrosine kinase inhibitor for an underlying malignancy who also had autoimmune diseases reported that the drugs also appeared to have positive effects on symptoms of autoimmune conditions [102]. Although the precise mechanism of the effect of imatinib on diabetes remains unclear, the beneficial effect appeared to be from the ability to block platelet-derived growth factor receptor [103]. Follow-up preclinical investigations suggested that imatinib might preserve beta cells by counteracting high levels of endoplasmic reticulum stress in beta cells [104]. In a multicentre, randomized, double-blind, placebo-controlled, phase 2 trial, participants with recent-onset T1D (<100 days from diagnosis), aged 18–45 years were randomly assigned (2:1) to receive either 400 mg imatinib mesylate (4 × 100 mg film-coated tablets per day) or matching placebo for 26 weeks. Forty-five participants were assigned to receive imatinib and 22 to receive placebo. After withdrawals, 43 participants in the imatinib group and 21 in the placebo group were included in the analysis at 12 months. The adjusted difference in the AUC mean for C-peptide response in the first 2 h of a 4-h MMTT at 12 months in the imatinib group versus the placebo group was 0.095 nmol/L (p = 0.048). This effect was not sustained at 24 months. The most common adverse events were gastrointestinal issues. Seventeen (38%) participants in the imatinib group required a temporary modification in drug dosing, and 6 (13%) permanently discontinued imatinib due to adverse events. Therefore, treated participants should be monitored closely for potential side effects and toxicities that require modification to imatinib dosing [105].

Auto-Antigen-Based Therapy

Insulin is a key autoantigen in T1D. Since antigen can induce clonal deletion or anergy of T-cells and activation of Tregs when it encounters oral or nasal mucosa, antigen-specific immunotherapy aims at generating a regulatory immune response against insulin. Several studies have tested oral insulin in individuals with pre-symptomatic autoantibody-positive T1D. There have been no significant safety concerns regarding oral/intranasal insulin use. Although none of the trials have reached their primary endpoints, some delay in progression to T1D was observed within treated groups [106]. A post hoc analysis combined findings from the two large trials in pre-symptomatic autoantibody-positive individuals [107, 108] and used risk scores, including age, body mass index, and glucose tolerance, to identify participants at higher risk for diabetes. Using this stratification in those with the highest risk for T1D, the oral insulin group had a significantly higher AUC C-peptide/AUC glucose ratio after 12 months of treatment. This study demonstrated that oral insulin slows the metabolic decline in participants with increased risk and may be restricted to a later stage of pre-symptomatic T1D [109].

Insulin has also been administered orally in primary prevention trials. Recently, results of the phase I/II randomized controlled Pre-POInT-early trial were published. Forty-four young islet autoantibody-negative children (aged 6 months to 2.99 years) who had a first-degree relative with T1D and a susceptible HLA-DR4-DQ8-containing genotype were treated with escalating doses of oral insulin or placebo for 12 months. Immune responses to insulin (antibody or T-cell responses) were not significantly different from placebo (p = 0.54); thus, the trial did not demonstrate an effect on its primary outcome. However, exploratory analyses revealed that the insulin gene (INS) genotype modified the immune response and gut microbiome. In children with the T1D-susceptible INS genotype, antibody responses to insulin were more frequent in insulin-treated than placebo-treated children (p = 0.03). There were no adverse effects related to the therapy [110]. The Global Platform of Autoimmune Diabetes – Primary Oral Insulin Trial (GPPAD-POInT) is designed as a large randomized, placebo-controlled, double-blind, primary prevention phase II b study. Very young

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children (age 4 months to 7 months) with elevated genetic risk for T1D will be treated with daily oral insulin in escalated doses until age 3 years to determine whether this will induce immune tolerance to beta-cell autoantigens and reduce the cumulative incidence of beta-cell autoantibodies and diabetes in childhood (NCT03364868) [111].

A multicentre, randomized, placebo-controlled, double-blind phase 2b trial (DIAGNODE-2) evaluated efficacy of intra-lymphatic administration of GAD, a self-antigen expressed by beta cells, combined with alum hydroxide to form GAD-alum (Diamyd®) [112]. A total of 109 GAD autoantibody-positive individuals, aged 12–24 years (mean ± SD 16.4 ± 4.1) diagnosed with T1D within 6 months prior to screening were randomized to receive either GAD-alum or placebo directly into the superficial lymph node on three occasions, 1 month apart, in combination with oral vitamin D 2,000 IE daily for 120 days (or its placebo), starting 30 days prior to the first injection. The primary outcome was the change in stimulated serum C-peptide AUC after a mixed-meal tolerance test between baseline and 15 months. Since previous placebo-controlled trials [113] indicated that the response was best in participants positive for HLA-DR3-DQ2, but negative for DR4-DQ8 haplotype, individuals carrying the HLA-DR3-DQ2 haplotype were predefined as a specific subpopulation for safety and efficacy evaluation. The primary endpoint of change in stimulated serum C-peptide was not met in the full analysis set. However, the treatment showed significant effect on preservation of C-peptide in a genetically defined subgroup carrying HLA-DR3-DQ2 haplotype. Intra-lymphatic GAD-alum administration presented a good safety profile with minor transient injection site reactions [112]. The upcoming phase 3 trial will evaluate the efficacy shown in the DIAGNODE-2 in a larger number of adolescents and adults recently diagnosed with T1D carrying the HLA-DR3-DQ2 haplotype [114].

Challenges and Future Perspectives

Several immune therapies have demonstrated significant but short-term capacity to preserve beta-cell function in individuals with new-onset T1D. In a cross-trial comparison of seven immunotherapy trials, low-dose ATG and teplizumab had the most significant beneficial effect on C-peptide retention in individuals with new-onset T1D [115]. These data suggest that teplizumab and low-dose ATG could be used as high efficacy initial treatment to stop the immune system attack on beta cells. However, since instant and durable disease remission might be unlikely after discontinuation, immunomodulatory interventions may have to be continued indefinitely [116]. Synergistic combinations of immunotherapy agents targeting different types of immune responses might have better potential to induce lasting remission or at least improve safety and efficacy. As immunotherapy alone might not be sufficient [117], interventions that alleviate beta-cell stress and directly contribute to the functional beta-cell mass, such as liraglutide, verapamil, and tyrosine kinase inhibitors, are being evaluated.

Future studies should address several important aspects of immune interventions in T1D to successfully implement them in a clinical setting. Firstly, the heterogeneity of T1D is an important aspect to be considered. For example, children developing T1D have a more aggressive disease with less residual beta-cell function at presentation. Surprisingly, immunotherapies appear more effective in individuals with younger age at onset. Furthermore, most intervention trials of disease-modifying therapies with some positive impact on beta-cell preservation had only transient effect on halting the progressive autoimmune reaction against beta cells. However, analyses in some interventions have shown heterogeneity in response to therapy and identified subgroups of individuals with a good clinical outcome [45, 50, 60, 108, 113]. Therefore, further knowledge of underlying pathophysiological mechanisms may be important to adequately define subtypes of T1D and successfully implement personalized medicine. Since one single treatment might not be appropriate for everyone, individual choices of intervention strategies for high-risk pre-symptomatic or newly diagnosed individuals may have to be considered for a better outcome. The teplizumab prevention trial results support the notion that immune-modulating therapies should focus on high-risk non-diabetic individuals with early signs of islet autoimmunity to prevent or delay T1D. Indeed, treatments that have already been proven effective in preserving beta-cell function in recent-onset T1D are being studied in preventive interventions. In addition, the forthcoming availability of immunotherapy in pre-symptomatic stages of T1D will accelerate the implementation of population-based screening programmes. Well-established immune and metabolic biomarkers of T1D such as autoantibodies and C-peptide levels may be too robust to precisely define disease progression and rapidly detect the beneficial effect of a given immune intervention. Therefore, new assays using novel biomarkers are being developed to assess the heterogeneity of T1D progression and response to immunotherapies [118]. Finally,

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a clinically meaningful benefit for people at risk or already living with T1D should not be limited to achieving reasonable glycaemic control. It is essential to also consider the quality of life metrics and other patient-reported outcomes as crucial clinical outcomes.

Conflict of Interest Statement

The author has no conflicts of interest to declare.

Funding Sources

D.S.S. was funded in part by the Slovenian Research Agency grant P3-0343.

Author Contributions

Darja Smigoc Schweiger was responsible for originating the idea for the manuscript, concept development, and writing of the manuscript.

References

1 International Diabetes Federation. IDF diabetes atlas [Internet]. 9th ed. Brussels, Belgium; 2019 [cited 2021 Oct 9]. Available from: https: //diabetesatlas.org/idfawp/resource-files/2019/07/IDF_diabetes_atlas_ninth_edition_en.pdf.
2 Dovc K, Battelino T. Evolution of diabetes technology. Endocrinol Metab Clin North Am. 2020;49(1):1–18.
3 Dovc K, Telic SS, Lusa L, Bratanic N, Zerjav-Tansek M, Kotnik P, et al. Improved metabolic control in pediatric patients with type 1 diabetes: a nationwide prospective 12-year time trends analysis. Diabetes Technol Ther. 2014;16(1):33–40.
4 Lind M, Svensson AM, Kosiborod M, Gudbjörnsdottir S, Pivodic A, Wedel H, et al. Glycemic control and excess mortality in type 1 diabetes. N Engl J Med. 2014;371(21):1972–82.
5 Smigoc Schweiger D, Mendez A, Kunilo Jamnik S, Bratanic N, Bratina N, Battelino T, et al. High-risk genotypes HLA-DR3-DQ2/DR3-DQ2 and DR3-DQ2/DR4-DQ8 in co-occurrence of type 1 diabetes and celiac disease. Autoimmunity. 2016;49(4):240–7.
6 Bluestone JA, Herold K, Eisenbarth G. Genetics, pathogenesis and clinical interventions in type 1 diabetes. Nature. 2010;464(7293):1293–300.
7 Atkinson MA, Eisenbarth GS, Michels AW. Type 1 diabetes. Lancet. 2014;383(9911):69–82.
8 Coppieters KT, Dotta F, Amirian N, Campbell PD, Kay TW, Atkinson MA, et al. Demonstration of islet-autoreactive CD8 T cells in insulitic lesions from recent onset and long-term type 1 diabetes patients. J Exp Med. 2012;209(1):51–60.
9 Peakman M. Immunological pathways to β-cell damage in Type 1 diabetes. Diabet Med. 2013;30(2):147–54.
10 Brusko TM, Wasserfall CH, Clare-Salzler MJ, Schatz DA, Atkinson MA. Functional defects and the influence of age on the frequency of CD4+ CD25+ T-cells in type 1 diabetes. Diabetes. 2005;54(5):1407–14.
11 Lindley S, Dayan CM, Bishop A, Roep BO, Peakman M, Tree TI. Defective suppressor function in CD4(+)CD25(+) T-cells from patients with type 1 diabetes. Diabetes. 2005;54(1):92–9.
12 Ziegler AG, Nepom GT. Prediction and pathogenesis in type 1 diabetes. Immunity. 2010;32(4):468–78.
13 Parikka V, Näntö-Salonen K, Saarinen M, Simell T, Ilonen J, Hyöty H, et al. Early seroconversion and rapidly increasing autoantibody concentrations predict prepubertal manifestation of type 1 diabetes in children at genetic risk. Diabetologia. 2012;55(7):1926–36.
14 Ziegler AG, Rewers M, Simell O, Simell T, Lempainen J, Steck A, et al. Seroconversion to multiple islet autoantibodies and risk of progression to diabetes in children. JAMA. 2013;309(23):2473–9.
15 Insel RA, Dunne JL, Atkinson MA, Chiang JL, Dabelea D, Gottlieb PA, et al. Staging presymptomatic type 1 diabetes: a scientific statement of JDRF, the Endocrine Society, and the American Diabetes Association. Diabetes Care. 2015;38(10):1964–74.
16 Battaglia M, Ahmed S, Anderson MS, Atkinson MA, Becker D, Bingley PJ, et al. Introducing the endotype concept to address the challenge of disease heterogeneity in type 1 diabetes. Diabetes Care. 2020;43(1):5–12.
17 Krischer JP, Lynch KF, Lernmark Å, Hagopian WA, Rewers MJ, She JX, et al. Genetic and environmental interactions modify the risk of diabetes-related autoimmunity by 6 years of age: the TEDDY study. Diabetes Care. 2017;40(9):1194–202.
18 Ilonen J, Lempainen J, Hammais A, Laine AP, Härkönen T, Toppari J, et al. Primary islet autoantibody at initial seroconversion and autoantibodies at diagnosis of type 1 diabetes as markers of disease heterogeneity. Pediatr Diabetes. 2018;19(2):284–92.
19 Leete P, Willcox A, Krogvold L, Dahl-Jørgensen K, Foulis AK, Richardson SJ, et al. Differential insulitic profiles determine the extent of β-cell destruction and the age at onset of type 1 diabetes. Diabetes. 2016;65(5):1362–9.
20 Leete P, Oram RA, McDonald TJ, Shields BM, Ziller C, Hattersley AT, et al. Studies of insulin and proinsulin in pancreas and serum support the existence of aetiopathological endotypes of type 1 diabetes associated with age at diagnosis. Diabetologia. 2020;63(6):1258–67.
21 Skyler JS. Primary and secondary prevention of type 1 diabetes. Diabet Med. 2013;30(2):161–9.
22 Skyler JS, Bakris GL, Bonifacio E, Darsow T, Eckel RH, Groop L, et al. Differentiation of diabetes by pathophysiology, natural history, and prognosis. Diabetes. 2017;66(2):241–55.
23 Nwosu BU, Zhang B, Ayyoub SS, Choi S, Villalobos-Ortiz TR, Alonso LC, et al. Children with type 1 diabetes who experienced a honeymoon phase had significantly lower LDL cholesterol 5 years after diagnosis. PLoS One. 2018;13(5):e0196912.
24 Skyler JS. Prevention and reversal of type 1 diabetes – past challenges and future opportunities. Diabetes Care. 2015;38(6):997–1007.
25 Wang P, Fiaschi-Taesch NM, Vasavada RC, Scott DK, García-Ocaña A, Stewart AF. Diabetes mellitus – advances and challenges in human β-cell proliferation. Nat Rev Endocrinol. 2015;11(4):201–12.
26 Bingley PJ, Wherrett DK, Shultz A, Rafkin LE, Atkinson MA, Greenbaum CJ. Type 1 diabetes TrialNet: a multifaceted approach to bringing disease-modifying therapy to clinical use in type 1 diabetes. Diabetes Care. 2018;41(4):653–61.
27 INNODIA [Internet] [cited 2021 Oct 4]. Available from: https://www.innodia.eu/.
28 Genzyme Corporation. Thymoglobulin prescribing information [Internet]. Cambridge, MA: Genzyme Corporation [updated 2020 April; cited 2021 Oct 4]. Available from: https: //products.sanofi.us/thymoglobulin/thymoglobulin.pdf.
29 LaCorcia G, Swistak M, Lawendowski C, Duan S, Weeden T, Nahill S, et al. Polyclonal rabbit antithymocyte globulin exhibits consistent immunosuppressive capabilities beyond cell depletion. Transplantation. 2009;87(7):966–74.
30 Bamoulid J, Crépin T, Courivaud C, Rebibou JM, Saas P, Ducloux D. Antithymocyte globulins in renal transplantation-from lymphocyte depletion to lymphocyte activation: the doubled-edged sword. Transplant Rev. 2017;31(3):180–7.

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31 Scheinberg P, Nunez O, Weinstein B, Scheinberg P, Biancotto A, Wu CO, et al. Horse versus rabbit antithymocyte globulin in acquired aplastic anemia. N Engl J Med. 2011;365(5):430–8.
32 Gitelman SE, Gottlieb PA, Rigby MR, Felner EI, Willi SM, Fisher LK, et al. Antithymocyte globulin treatment for patients with recent-onset type 1 diabetes: 12-month results of a randomised, placebo-controlled, phase 2 trial. Lancet Diabetes Endocrinol. 2013;1(4):306–16.
33 Haller MJ, Gitelman SE, Gottlieb PA, Michels AW, Rosenthal SM, Shuster JJ, et al. Anti-thymocyte globulin/G-CSF treatment preserves β cell function in patients with established type 1 diabetes. J Clin Invest. 2015;125(1):448–55.
34 Haller MJ, Schatz DA, Skyler JS, Krischer JP, Bundy BN, Miller JL, et al. Low-dose anti-thymocyte globulin (ATG) preserves β-cell function and improves HbA(1c) in new-onset type 1 diabetes. Diabetes Care. 2018;41(9):1917–25.
35 Gitelman SE, Gottlieb PA, Felner EI, Willi SM, Fisher LK, Moran A, et al. Antithymocyte globulin therapy for patients with recent-onset type 1 diabetes: 2 year results of a randomised trial. Diabetologia. 2016;59(6):1153–61.
36 Haller MJ, Gitelman SE, Gottlieb PA, Michels AW, Perry DJ, Schultz AR, et al. Antithymocyte globulin plus G-CSF combination therapy leads to sustained immunomodulatory and metabolic effects in a subset of responders with established type 1 diabetes. Diabetes. 2016;65(12):3765–75.
37 Lin A, Mack JA, Bruggeman B, Jacobsen LM, Posgai AL, Wasserfall CH, et al. Low-dose ATG/GCSF in established type 1 diabetes: a five-year follow-up report. Diabetes. 2021;70(5):1123–9.
38 Haller MJ, Long SA, Blanchfield JL, Schatz DA, Skyler JS, Krischer JP, et al. Low-dose anti-thymocyte globulin preserves C-peptide, reduces HbA(1c), and increases regulatory to conventional T-cell ratios in new-onset type 1 diabetes: two-year clinical trial data. Diabetes. 2019;68(6):1267–76.
39 Universitaire Ziekenhuizen Leuven. MELD-ATG: phase II, dose ranging, efficacy study of anti-thymocyte globulin (ATG) within 6 weeks of diagnosis of type 1 diabetes (T1D) (Meld-ATG) [Internet]. Bethesda, MD: National Library of Medicine; 2020 [cited 2021 Oct 4]. Available from: https://clinicaltrials.gov/ct2/show/NCT04509791.
40 National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK). Low dose antithymocyte globulin (ATG) to delay or prevent progression to stage 3 T1D (TN28) [Internet]. Bethesda, MD: National Library of Medicine; 2020 [cited 2021 Oct 4]. Available from: https: //clinicaltrials.gov/ct2/show/NCT04291703.
41 Long SA, Thorpe J, DeBerg HA, Gersuk V, Eddy J, Harris KM, et al. Partial exhaustion of CD8 T cells and clinical response to teplizumab in new-onset type 1 diabetes. Sci Immunol. 2016;1(5):eaai7793.
42 Penaranda C, Tang Q, Bluestone JA. Anti-CD3 therapy promotes tolerance by selectively depleting pathogenic cells while preserving regulatory T cells. J Immunol. 2011;187(4):2015–22.
43 Carpenter PA, Pavlovic S, Tso JY, Press OW, Gooley T, Yu XZ, et al. Non-Fc receptor-binding humanized anti-CD3 antibodies induce apoptosis of activated human T cells. J Immunol. 2000;165(11):6205–13.
44 Herold KC, Hagopian W, Auger JA, Poumian-Ruiz E, Taylor L, Donaldson D, et al. Anti-CD3 monoclonal antibody in new-onset type 1 diabetes mellitus. N Engl J Med. 2002;346(22):1692–8.
45 Sherry N, Hagopian W, Ludvigsson J, Jain SM, Wahlen J, Ferry RJ Jr, et al. Teplizumab for treatment of type 1 diabetes (Protégé study): 1-year results from a randomised, placebo-controlled trial. Lancet. 2011;378(9790):487–97.
46 Hagopian W, Ferry RJ Jr, Sherry N, Carlin D, Bonvini E, Johnson S, et al. Teplizumab preserves C-peptide in recent-onset type 1 diabetes: two-year results from the randomized, placebo-controlled Protégé trial. Diabetes. 2013;62(11):3901–8.
47 Herold KC, Gitelman SE, Ehlers MR, Gottlieb PA, Greenbaum CJ, Hagopian W, et al. Teplizumab (anti-CD3 mAb) treatment preserves C-peptide responses in patients with new-onset type 1 diabetes in a randomized controlled trial: metabolic and immunologic features at baseline identify a subgroup of responders. Diabetes. 2013;62(11):3766–74.
48 Perdigoto AL, Preston-Hurlburt P, Clark P, Long SA, Linsley PS, Harris KM, et al. Treatment of type 1 diabetes with teplizumab: clinical and immunological follow-up after 7 years from diagnosis. Diabetologia. 2019;62(4):655–64.
49 Krischer JP. The use of intermediate endpoints in the design of type 1 diabetes prevention trials. Diabetologia. 2013;56(9):1919–24.
50 Herold KC, Bundy BN, Long SA, Bluestone JA, DiMeglio LA, Dufort MJ, et al. An anti-CD3 antibody, teplizumab, in relatives at risk for type 1 diabetes. N Engl J Med. 2019;381(7):603–13.
51 Sims EK, Bundy BN, Stier K, Serti E, Lim N, Long SA, et al. Teplizumab improves and stabilizes beta cell function in antibody-positive high-risk individuals. Sci Transl Med. 2021;13(583):eabc8980.
52 Provention Bio Inc. Recent-onset type 1 diabetes trial evaluating efficacy and safety of teplizumab (PROTECT) [Internet]. Bethesda, MD: National Library of Medicine; 2019 [cited 2021 Oct 4]. Available from: https://clinicaltrials.gov/ct2/show/NCT03875729.
53 Keymeulen B, Vandemeulebroucke E, Ziegler AG, Mathieu C, Kaufman L, Hale G, et al. Insulin needs after CD3-antibody therapy in new-onset type 1 diabetes. N Engl J Med. 2005;352(25):2598–608.
54 Keymeulen B, Walter M, Mathieu C, Kaufman L, Gorus F, Hilbrands R, et al. Four-year metabolic outcome of a randomised controlled CD3-antibody trial in recent-onset type 1 diabetic patients depends on their age and baseline residual beta cell mass. Diabetologia. 2010;53(4):614–23.
55 Aronson R, Gottlieb PA, Christiansen JS, Donner TW, Bosi E, Bode BW, et al. Low-dose otelixizumab anti-CD3 monoclonal antibody DEFEND-1 study: results of the randomized phase III study in recent-onset human type 1 diabetes. Diabetes Care. 2014;37(10):2746–54.
56 Ambery P, Donner TW, Biswas N, Donaldson J, Parkin J, Dayan CM. Efficacy and safety of low-dose otelixizumab anti-CD3 monoclonal antibody in preserving C-peptide secretion in adolescent type 1 diabetes: DEFEND-2, a randomized, placebo-controlled, double-blind, multi-centre study. Diabet Med. 2014;31(4):399–402.
57 MacDonald A, Ambery P, Donaldson J, Hicks K, Keymeulen B, Parkin J. Subcutaneous administration of otelixizumab is limited by injection site reactions: results of an exploratory study in type 1 diabetes mellitus patients. Exp Clin Endocrinol Diabetes. 2016;124(5):288–93.
58 Fife BT, Bluestone JA. Control of peripheral T-cell tolerance and autoimmunity via the CTLA-4 and PD-1 pathways. Immunol Rev. 2008;224:166–82.
59 Buch MH, Vital EM, Emery P. Abatacept in the treatment of rheumatoid arthritis. Arthritis Res Ther. 2008;10(Suppl 1):S5.
60 Orban T, Bundy B, Becker DJ, DiMeglio LA, Gitelman SE, Goland R, et al. Co-stimulation modulation with abatacept in patients with recent-onset type 1 diabetes: a randomised, double-blind, placebo-controlled trial. Lancet. 2011;378(9789):412–9.
61 Orban T, Beam CA, Xu P, Moore K, Jiang Q, Deng J, et al. Reduction in CD4 central memory T-cell subset in costimulation modulator abatacept-treated patients with recent-onset type 1 diabetes is associated with slower C-peptide decline. Diabetes. 2014;63(10):3449–57.
62 Orban T, Bundy B, Becker DJ, Dimeglio LA, Gitelman SE, Goland R, et al. Costimulation modulation with abatacept in patients with recent-onset type 1 diabetes: follow-up 1 year after cessation of treatment. Diabetes Care. 2014;37(4):1069–75.
63 Cabrera SM, Engle S, Kaldunski M, Jia S, Geoffrey R, Simpson P, et al. Innate immune activity as a predictor of persistent insulin secretion and association with responsiveness to CTLA4-Ig treatment in recent-onset type 1 diabetes. Diabetologia. 2018;61(11):2356–70.
64 National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK). CTLA4-Ig (Abatacept) for prevention of abnormal glucose tolerance and diabetes in relatives at -risk for type 1 [Internet]. Bethesda, MD: National Library of Medicine; 2013 [cited 2021 Oct 4]. Available from: https://www.clinicaltrials.gov/ct2/show/NCT01773707.

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65 Ellis CN, Krueger GG. Treatment of chronic plaque psoriasis by selective targeting of memory effector T lymphocytes. N Engl J Med. 2001;345(4):248–55.
66 Rigby MR, DiMeglio LA, Rendell MS, Felner EI, Dostou JM, Gitelman SE, et al. Targeting of memory T cells with alefacept in new-onset type 1 diabetes (T1DAL study): 12 month results of a randomised, double-blind, placebo-controlled phase 2 trial. Lancet Diabetes Endocrinol. 2013;1(4):284–94.
67 Rigby MR, Harris KM, Pinckney A, DiMeglio LA, Rendell MS, Felner EI, et al. Alefacept provides sustained clinical and immunological effects in new-onset type 1 diabetes patients. J Clin Invest. 2015;125(8):3285–96.
68 Hinman RM, Cambier JC. Role of B lymphocytes in the pathogenesis of type 1 diabetes. Curr Diab Rep. 2014;14(11):543.
69 Schioppo T, Ingegnoli F. Current perspective on rituximab in rheumatic diseases. Drug Des Devel Ther. 2017;11:2891–904.
70 Pescovitz MD, Greenbaum CJ, Krause-Steinrauf H, Becker DJ, Gitelman SE, Goland R, et al. Rituximab, B-lymphocyte depletion, and preservation of beta-cell function. N Engl J Med. 2009;361(22):2143–52.
71 Pescovitz MD, Greenbaum CJ, Bundy B, Becker DJ, Gitelman SE, Goland R, et al. B-lymphocyte depletion with rituximab and β-cell function: two-year results. Diabetes Care. 2014;37(2):453–9.
72 Yu L, Herold K, Krause-Steinrauf H, McGee PL, Bundy B, Pugliese A, et al. Rituximab selectively suppresses specific islet antibodies. Diabetes. 2011;60(10):2560–5.
73 Linsley PS, Greenbaum CJ, Rosasco M, Presnell S, Herold KC, Dufort MJ. Elevated T cell levels in peripheral blood predict poor clinical response following rituximab treatment in new-onset type 1 diabetes. Genes Immun. 2019;20(4):293–307.
74 National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK). Rituximab and abatacept for prevention or reversal of type 1 diabetes (TN25) [Internet]. Bethesda, MD: National Library of Medicine; 2019 [cited 2021 Oct 4]. Available from: https://clinicaltrials.gov/ct2/show/NCT03929601.
75 Peters NC, Kroeger DR, Mickelwright S, Bretscher PA. CD4 T cell cooperation is required for the in vivo activation of CD4 T cells. Int Immunol. 2009;21(11):1213–24.
76 Huber AK, Finkelman FD, Li CW, Concepcion E, Smith E, Jacobson E, et al. Genetically driven target tissue overexpression of CD40: a novel mechanism in autoimmune disease. J Immunol. 2012;189(6):3043–53.
77 Ristov J, Espie P, Ulrich P, Sickert D, Flandre T, Dimitrova M, et al. Characterization of the in vitro and in vivo properties of CFZ533, a blocking and non-depleting anti-CD40 monoclonal antibody. Am J Transplant. 2018;18(12):2895–904.
78 Mavragani CP, Moutsopoulos HM. Sjögren's syndrome: old and new therapeutic targets. J Autoimmun. 2020;110:102364.
79 Kahaly GJ, Stan MN, Frommer L, Gergely P, Colin L, Amer A, et al. A novel anti-CD40 monoclonal antibody, iscalimab, for control of Graves hyperthyroidism-a proof-of-concept trial. J Clin Endocrinol Metab. 2020;105(3.
80 Klein D, Barbé-Tuana F, Pugliese A, Ichii H, Garza D, Gonzalez M, et al. A functional CD40 receptor is expressed in pancreatic beta cells. Diabetologia. 2005;48(2):268–76.
81 Chatzigeorgiou AE, Lembessis PE, Mylona-Karagianni CF, Tsouvalas EA, Diamanti-Kandarakis E, Kamper EF. CD40 expression and its association with low-grade inflammation in a Greek population of type 1 diabetic juveniles: evidence for differences in CD40 mRNA isoforms expressed by peripheral blood mononuclear cells. Exp Clin Endocrinol Diabetes. 2010;118(1):38–46.
82 Novartis Pharmaceuticals. Study of safety and efficacy of CFZ533 in type 1 diabetes pediatric and young adult subjects (CCFZ533X2207) [Internet]. Bethesda, MD: National Library of Medicine; 2019 [cited 2021 Oct 4]. Available from: https: //clinicaltrials.gov/ct2/show/NCT04129528.
83 Dominguez-Villar M, Hafler DA. Regulatory T cells in autoimmune disease. Nat Immunol. 2018;19(7):665–73.
84 Marek-Trzonkowska N, Mysliwiec M, Dobyszuk A, Grabowska M, Techmanska I, Juscinska J, et al. Administration of CD4+CD25highCD127- regulatory T cells preserves β-cell function in type 1 diabetes in children. Diabetes Care. 2012;35(9):1817–20.
85 Bluestone JA, Buckner JH, Fitch M, Gitelman SE, Gupta S, Hellerstein MK, et al. Type 1 diabetes immunotherapy using polyclonal regulatory T cells. Sci Transl Med. 2015;7(315):315ra189.
86 Caladrius Biosciences Inc. Safety and efficacy of CLBS03 in adolescents with recent onset type 1 diabetes (The Sanford Project T-Rex Study) [Internet]. Bethesda, MD: National Library of Medicine; 2016 [cited 2021 Oct 4]. Available from: https://clinicaltrials.gov/ct2/show/NCT02691247.
87 Second Xiangya Hospital of Central South University. Safety and efficacy of umbilical cord blood regulatory T cells plus Liraglutide on autoimmune diabetes [Internet]. Bethesda, MD: National Library of Medicine; 2017 [cited 2021 Oct 4]. Available from: https://clinicaltrials.gov/ct2/show/NCT03011021.
88 Tahvildari M, Dana R. Low-dose IL-2 therapy in transplantation, autoimmunity, and inflammatory diseases. J Immunol. 2019;203(11):2749–55.
89 Rosenzwajg M, Salet R, Lorenzon R, Tchitchek N, Roux A, Bernard C, et al. Low-dose IL-2 in children with recently diagnosed type 1 diabetes: a phase I/II randomised, double-blind, placebo-controlled, dose-finding study. Diabetologia. 2020;63(9):1808–21.
90 University of Oxford. Interleukin-2 therapy of autoimmunity in diabetes (ITAD) (ITAD) [Internet]. Bethesda, MD: National Library of Medicine; 2018 [cited 2021 Oct 4]. Available from: https://clinicaltrials.gov/ct2/show/NCT03782636.
91 Dong S, Hiam-Galvez KJ, Mowery CT, Herold KC, Gitelman SE, Esensten JH, et al. The effect of low-dose IL-2 and Treg adoptive cell therapy in patients with type 1 diabetes. JCI Insight. 2021;6(18):e147474.
92 Bender C, Rajendran S, von Herrath MG. New insights into the role of autoreactive CD8 T cells and cytokines in human type 1 diabetes. Front Endocrinol. 2020;11:606434.
93 Siebert S, Tsoukas A, Robertson J, McInnes I. Cytokines as therapeutic targets in rheumatoid arthritis and other inflammatory diseases. Pharmacol Rev. 2015;67(2):280–309.
94 Jang DI, Lee AH, Shin HY, Song HR, Park JH, Kang TB, et al. The role of tumor necrosis factor alpha (TNF-α) in autoimmune disease and current TNF-α inhibitors in therapeutics. Int J Mol Sci. 2021;22(5):2719.
95 Mastrandrea L, Yu J, Behrens T, Buchlis J, Albini C, Fourtner S, et al. Etanercept treatment in children with new-onset type 1 diabetes: pilot randomized, placebo-controlled, double-blind study. Diabetes Care. 2009;32(7):1244–9.
96 Quattrin T, Haller MJ, Steck AK, Felner EI, Li Y, Xia Y, et al. Golimumab and beta-cell function in youth with new-onset type 1 diabetes. N Engl J Med. 2020;383(21):2007–17.
97 Long D, Chen Y, Wu H, Zhao M, Lu Q. Clinical significance and immunobiology of IL-21 in autoimmunity. J Autoimmun. 2019;99:1–14.
98 Ignatenko S, Skrumsager BK, Mouritzen U. Safety, PK, and PD of recombinant anti-interleukin-21 monoclonal antibody in a first-in-human trial. Int J Clin Pharmacol Ther. 2016;54(4):243–52.
99 Dejgaard TF, von Scholten BJ, Christiansen E, Kreiner FF, Bardtrum L, von Herrath M, et al. Efficacy and safety of liraglutide in type 1 diabetes by baseline characteristics in the ADJUNCT ONE and ADJUNCT TWO randomized controlled trials. Diabetes Obes Metab. 2021;23(12):2752–62.
100 von Herrath M, Bain SC, Bode B, Clausen JO, Coppieters K, Gaysina L, et al. Anti-interleukin-21 antibody and liraglutide for the preservation of β-cell function in adults with recent-onset type 1 diabetes: a randomised, double-blind, placebo-controlled, phase 2 trial. Lancet Diabetes Endocrinol. 2021;9(4):212–24.
101 Zhang J, Yang PL, Gray NS. Targeting cancer with small molecule kinase inhibitors. Nat Rev Cancer. 2009;9(1):28–39.
102 Huda MS, Amiel SA, Ross P, Aylwin SJ. Tyrosine kinase inhibitor sunitinib allows insulin independence in long-standing type 1 diabetes. Diabetes Care. 2014;37(5):e87–8.

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103 Louvet C, Szot GL, Lang J, Lee MR, Martinier N, Bollag G, et al. Tyrosine kinase inhibitors reverse type 1 diabetes in nonobese diabetic mice. Proc Natl Acad Sci U S A. 2008;105(48):18895–900.
104 Morita S, Villalta SA, Feldman HC, Register AC, Rosenthal W, Hoffmann-Petersen IT, et al. Targeting ABL-IRE1α signaling spares ER-stressed pancreatic β cells to reverse autoimmune diabetes. Cell Metab. 2017;25(4):883–97.e8.
105 Gitelman SE, Bundy BN, Ferrannini E, Lim N, Blanchfield JL, DiMeglio LA, et al. Imatinib therapy for patients with recent-onset type 1 diabetes: a multicentre, randomised, double-blind, placebo-controlled, phase 2 trial. Lancet Diabetes Endocrinol. 2021;9(8):502–14.
106 Jacobsen LM, Schatz DA. Insulin immunotherapy for pretype 1 diabetes. Curr Opin Endocrinol Diabetes Obes. 2021;28(4):390–6.
107 Skyler JS, Krischer JP, Wolfsdorf J, Cowie C, Palmer JP, Greenbaum C, et al. Effects of oral insulin in relatives of patients with type 1 diabetes: the diabetes prevention trial – type 1. Diabetes Care. 2005;28(5):1068–76.
108 Krischer JP, Krischer JP, Schatz DA, Bundy B, Skyler JS, Greenbaum CJ. Effect of oral insulin on prevention of diabetes in relatives of patients with type 1 diabetes: a randomized clinical trial. JAMA. 2017;318(19):1891–902.
109 Sosenko JM, Skyler JS, Herold KC, Schatz DA, Haller MJ, Pugliese A, et al. Slowed metabolic decline after 1 year of oral insulin treatment among individuals at high risk for type 1 diabetes in the diabetes prevention trial-type 1 (DPT-1) and TrialNet oral insulin prevention trials. Diabetes. 2020;69(8):1827–32.
110 Assfalg R, Knoop J, Hoffman KL, Pfirrmann M, Zapardiel-Gonzalo JM, Hofelich A, et al. Oral insulin immunotherapy in children at risk for type 1 diabetes in a randomised controlled trial. Diabetologia. 2021;64(5):1079–92.
111 Technische Universität München. GPPAD-POInT (Global platform of autoimmune diabetes: primary oral insulin trial) [Internet]. Bethesda, MD: National Library of Medicine; 2017 [cited 2021 Oct 4]. Available from: https://clinicaltrials.gov/ct2/show/NCT03364868.
112 Ludvigsson J, Sumnik Z, Pelikanova T, Nattero Chavez L, Lundberg E, Rica I, et al. Intralymphatic glutamic acid decarboxylase with vitamin D supplementation in recent-onset type 1 diabetes: a double-blind, randomized, placebo-controlled phase IIb trial. Diabetes Care. 2021;44(7):1604–12.
113 Hannelius U, Beam CA, Ludvigsson J. Efficacy of GAD-alum immunotherapy associated with HLA-DR3-DQ2 in recently diagnosed type 1 diabetes. Diabetologia. 2020;63(10):2177–81.
114 Diamyd Medical AB. Diamyd administered into lymph nodes in individuals recently diagnosed with type 1 diabetes, carrying the HLA DR3-DQ2 haplotype (DIAGNODE-3) [Internet]. Bethesda, MD: National Library of Medicine. 2021 [cited 2021 Oct 4]. Available from: https://clinicaltrials.gov/ct2/show/NCT05018585.
115 Jacobsen LM, Bundy BN, Greco MN, Schatz DA, Atkinson MA, Brusko TM, et al. Comparing beta cell preservation across clinical trials in recent-onset type 1 diabetes. Diabetes Technol Ther. 2020;22(12):948–53.
116 Skyler JS. New insights into halting type 1 diabetes. Lancet Diabetes Endocrinol. 2021;9(8):475–6.
117 Roep BO, Thomaidou S, van Tienhoven R, Zaldumbide A. Type 1 diabetes mellitus as a disease of the β-cell (do not blame the immune system?). Nat Rev Endocrinol. 2021;17(3):150–61.
118 Mathieu C, Lahesmaa R, Bonifacio E, Achenbach P, Tree T. Immunological biomarkers for the development and progression of type 1 diabetes. Diabetologia. 2018;61(11):2252–8.

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