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REVIEW

Immunotherapies for prevention and treatment of type 1 diabetes

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ABSTRACT

Type 1 diabetes (T1D) is characterized by the autoimmune destruction of insulin-producing β-cells of the pancreatic islets necessitating lifelong insulin therapy. Despite significant advancements in diabetes technology with increasingly sophisticated methods of insulin delivery and glucose monitoring, people with T1D remain at risk of severe complications like hypoglycemia and diabetic ketoacidosis. There has long been an interest in altering the immune response in T1D to prevent or cure T1D across its various stages with limited efficacy. This review highlights immunomodulatory approaches over the years including the anti-CD3 monoclonal antibody teplizumab which is now approved to delay onset of T1DM and other interventions under current investigation.

PLAIN LANGUAGE SUMMARY

Type 1 diabetes (T1D) is a chronic disease in which the immune system attacks insulin-producing cells in the pancreas, causing eventual complete dependence on insulin injections or insulin delivery devices like insulin pumps. Although insulin allows for better management of the disease, it does not prevent serious complications. Much research has gone into the factors that contribute to T1D particularly with regards to abnormal actions of the immune system, which has led researchers to explore new treatments targeting the disease at different stages. This review discusses different types of immunotherapies with the goal of preventing or treating T1D. One significant breakthrough is teplizumab, which was approved by the US Food and Drug Administration in 2022 to delay the progression of T1D in patients at high risk of developing T1D. While these new therapies show promise, achieving long-lasting control of blood sugar levels and the possibility of stopping insulin use remains difficult. Ongoing research aims to improve these treatments and find the best candidates for them, highlighting the importance of continued efforts in this area.

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1. Introduction

Although Type 1 diabetes (T1D) is a chronic autoimmune condition, it also represents the end stage of a multifactorial process, including both genetic and environmental factors that lead to the immune-mediated destruction of the insulin-producing β-cells of the pancreas. This ultimately results in the inability to regulate blood sugar concentrations without the administration of exogenous insulin. The isolation of insulin by Banting and Best profoundly changed the disease from a fatal diagnosis to a chronic condition manageable by multiple daily insulin injections or continuous infusion via increasingly advanced insulin delivery systems [1]. Though insulin is life-saving in patients with T1D, it does not serve as a cure and many patients still struggle with severe complications like hypoglycemia, diabetic ketoacidosis, and the various vascular comorbidities associated with diabetes. The understanding of the autoimmune underpinnings of T1D dates to the 1960–70s [2–4] and over the ensuing decades there has been an ever-expanding body of knowledge of the role of the immune system and contributions of genetic and environmental factors involved in the pathogenesis of T1D. This work has yielded a variety of potential therapeutic targets. Age and stages of T1D at which the interventions are provided do seem to affect efficacy, but the direction of influence varies. A consensus statement in 2015 from Breakthrough T1D (formerly the Juvenile Diabetes Research Foundation), the Endocrine Society, and the American Diabetes Association defined Stage 1 as the presence of two or more T1D-associated islet autoantibodies with normoglycemia, Stage 2 as the progression to glucose intolerance from loss of functional β-cell mass, and Stage 3 as further progression to the typical clinical symptoms and signs of diabetes [5]. In this review, the efforts at using immunological therapies that have reached the clinical arena to prevent and treat T1D at its different stages will be highlighted. A narrative literature review utilizing PubMed/MEDLINEdatabase was performed using the keywords “immunotherapy” with “type 1 diabetes.” Searches on subtopics regarding different therapeutics were also completed using a similar methodology.

2. Non-specific immunosuppressants

Early interest in broad immunosuppressive agents led to clinical studies with cyclosporin, azathioprine with prednisone, and methotrexate. Cyclosporin became the first

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Article highlights

- Overview of T1D: Type 1 diabetes is a chronic autoimmune condition that leads to the destruction of insulin-producing β-cells in the pancreas. Patients can manage the disease with insulin, but they are reliant on insulin for their entire lives and it does not treat the underlying autoimmunity which drives the disease.
  - Immunotherapy approaches have included:
  - Non-specific immunosuppressants
  - Antigen-based therapies
  - Anti-CD3 monoclonal antibodies
  - Costimulation blockade
- Research Challenges: Long-term independence from insulin and significant improvement in glycemic control has remained difficult to attain.
- Future Directions: Continued research is needed to refine treatment strategies, identify suitable candidates for therapies, and explore new immunotherapeutic agents.

immunosuppressive agent used in clinical trials of patients recently diagnosed with T1D [6,7]. There was temporary remission with preservation of residual β-cell function but due to the high doses required to induce remission, clinically significant nephrotoxicity, increased infections, and the swift return of the disease with treatment cessation limited the utility [8]. A small pilot study showed promising results with low-dose cyclosporine in tandem with low-dose methotrexate inducing remission in new onset T1D in children, with several able to stay off insulin during the 12 months of the study [9] but methotrexate alone was ineffective and possibly associated with even an earlier increase in insulin requirements [10]. Azathioprine and prednisone [11], azathioprine alone [12,13], and prednisone alone [14] showed some degree of delay in progression of T1D based on changes in plasma C-peptide (a peptide release from ß cells during cleavage of insulin from proinsulin used as a surrogate biomarker of ß cell function) and insulin-free months in some cases but again the long-term toxicities of immunosuppression and recurrence of disease after withdrawal of the immunosuppressive agents has limited the widespread use of these agents in T1D.

3. Antigen-based therapies

A complex array of precipitating factors including environmental exposure, the gut microbiome, and host genetic susceptibility are thought to contribute to pancreatic tissue destruction mainly driven by T cells with the release of self-antigen from destruction of pancreatic islets that are loaded to antigen-presenting cells and presented to antigen-specific T cells that then cause further damage to the pancreatic islets [15]. This peripheral loss of tolerance has been identified for β-cell proteins such as insulin, glutamic acid decarboxylase 65 (GAD65), insulinoma-associated-2 (IA-2), and Zinc Transporter T8 [16].

Antigen-based therapies, particularly those geared toward induction of passive tolerance by anergy of pathogenic T cells, were some of the next therapeutic attempts with the idea that they may promote tolerance with less overall suppression of the immune system. Administration of parenteral, intranasal, and oral insulin has not been successful in preventing or delaying the onset of T1D except for a subpopulation with high insulin autoantibody (IAA) levels that experienced delayed onset with oral insulin [17–23]. Concerningly, two studies of oral insulin found tendencies toward more rapid decline in basal C-peptide, in younger subjects and those treated with higher doses of oral insulin [22,24] which raised the question if these interventions actually accelerated the disease process in certain patient populations.

Stage 1 disease commonly includes the appearance of antibodies against glutamic acid decarboxylase 65 (GAD65) which are associated with the HLA DR3-DQ2 haplotype and destruction of pancreatic islet β cells once there is T cell recognition [25–27]. Preclinical data showed small amounts of GAD65 could prevent β cell destruction and delay the development of autoimmune diabetes in the non-obese diabetic mouse model [25,28–31]. The initial clinical trials of subcutaneous alum-formulated human recombinant GAD65 (rhGAD65/alum) were first carried out in individuals with latent autoimmune diabetes of adulthood (LADA), an adult-onset form of autoimmune diabetes sharing multiple characteristics with type 1 diabetes like some HLA genetic susceptibility and certain autoantibodies though β cell function tends to be higher at baseline in LADA patients [32]. C-peptide secretion increased over baseline 1 and 5 years in the 20-µg rhGAD65/alum treatment group with an increase in the $CD4^+CD25^+/CD4^+CD25^-$ cell ratio and the intervention seemed to be well-tolerated [32,33]. This dose also seemed to be effective in recently diagnosed (<6 months) children with T1D and resulted in greater preservation of fasting and stimulated C-peptide levels after 15 months [34]. Higher IL-5, IL-10, and IL-13 GAD-specific responses and frequencies of $Foxp3^+$ and TGFβ-secreting T-cells were seen after 15 months as well [34]. Similarly to the patients with higher IAA levels with a more robust response to oral insulin, those with higher baseline levels of GAD65 levels had improved preservation of C-peptide levels [35]. Additional analysis of the trials with rhGAD65/alum showed patients who specifically carried the HLA DR3-DQ2 haplotype but negative for the HLA-DR4-DQ8 haplotype showed a significant and dose-dependent improvement in preservation of β cell function as measured by C-peptide retention [34,36–39]. Phase I and II trials using an intralymphatic route of administering rhGAD65/alum in recent-onset T1D patients [40,41] again showed more promising results in HLA DR3-DQ2 carriers but not in the overall study population and is now in a Phase III study to evaluate efficacy in this specific population representing an early entrant into a precision medicine-based approach to T1D. Based on this work, rhGAD65/alum (Diamyd®) received Fast Track designation by the United States Food and Drug Administration in February 2024 [42,43].

Another approach has been with administration of modified insulin-derived peptides to generate antigen-specific cytolytic CD4+ T cells with effector memory phenotype to specifically eliminate antigen-presenting cells (APCs) presenting this epitope and eliminate autoreactive pathogenic T cells directed against this epitope and other epitopes presented on the same APC with the goal of protecting β-cells from autoimmunity [44–47]. Early clinical studies have demonstrated

Table 1. Ongoing clinical trials of immunotherapy approaches to type 1 diabetes.

Agent/Therapy	Official Study Name	ClinicalTrials.gov ID	Study Type	Estimated Patient Number	Eligible Age Range (years old)	Start Date	Estimated Completion
Autologous Regulary T cells	Clinical Safety and Therapeutic Effects of Autologous Tregs in T1D	NCT06708780	Phase I; Open label; Single-center	20	8–65	April 2023	December 2027
Bacillus Calmette-Guérin (BCG) vaccinations	Repeat BCG Vaccinations for the Treatment of New Onset Type 1 Diabetes in Children Age 8-<18 Years	NCT05866536	Phase II; Randomized; Triple-blinded; Single-center	100	8–18	May 2023	May 2028
BCG vaccinations	Repeat BCG Vaccinations for the Treatment of Established Type 1 Diabetes	NCT02081326	Phase II; Randomized; Triple-blinded; Single-center	150	18–65	June 2015	July 2031
CePolyTregs in Islet Transplantation	Cryopreserved Polyclonal Regulatory T Cell (cePolyTregs) Immunotherapy in Islet Transplantation	NCT05349591	Phase I; Non-Randomized; Open label; Single-center	11	18–68	August 2022	May 2025
Ciclosporin	Clinical and Biological Responses to Repeated Administration of Low-dose Interleukin-2 in Patients with Type 1 Diabetes and a Residual Insulin Secretion	NCT05153070	Phase II; Randomized; Double-blinded; Single-center	24	16–45	September 2022	April 2028
Diamyd	A Phase III, Randomized, Double-blind, Placebo-controlled, Multicenter Trial to Evaluate the Efficacy and Safety of Diamyd® to Preserve Endogenous Beta Cell Function in Adolescents and Adults with Recently Diagnosed Type 1 Diabetes, Carrying the Genetic HLA DR3-DQ2 Haplotype	NCT05018585	Phase III; Randomized; Quadruple-blinded; Single-center	330	12–28	May 2022	December 2027
Frexalimab	A 52-week Randomized, Double-blind, Placebo-controlled, Multi-center Phase 2b Study With a 52-week Blinded Extension Assessing Safety and Efficacy of Frexalimab, a CD40L-antagonist Monoclonal Antibody, for Preservation of Pancreatic β-cell Function in Adults and Adolescents With Newly Diagnosed Type 1 Diabetes on Insulin Therapy	NCT06111586	Phase II; Randomized; Double-blinded; Multicenter	192	12–35	December 2023	October 2028
JAK Inhibitors (abrocitnib, ritlecitinib)	A Phase 2 Multi-Center, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Safety and Efficacy of Subtype-Selective JAK Inhibitors for Preservation of Pancreatic B Cell Function in Newly Diagnosed Type 1 Diabetes Mellitus	NCT05743244	Phase II; Randomized; Double-blinded; Multicenter	78	12–35	October 2023	June 2027
Siplizumab	A T Cell Phenotype Signature Driven Dose Finding Study With Siplizumab in Type 1 Diabetes Mellitus (ITN095AI)	NCT05574335	Phase Ib; Open-label; Multicenter	120	8–45	April 2023	December 2027
Siplizumab	A 12-month, Randomized, Single-blind, Placebo-controlled Exposure-response Study of TCD601 (Siplizumab) in New Onset Type 1 Diabetes Patients (STRIDE)	NCT06025110	Phase II; Randomized; Single-blinded; Multicenter	96	18–45	January 2023	January 2025
Tolerogenic Dendritic Cell	A Pilot Study to Evaluate the Safety and Feasibility of Autologous Tolerogenic Dendritic Cells Loaded With Proinsulin Peptide (C19-A3) in Patients With Type 1 Diabetes	NCT04590872	Phase I; Open label; Single-center	6	18–45	June 2022	June 2025
UP421	First-in-human Safety Study of Hypoimmune Pancreatic Islet Transplantation in Adult Subjects With Type 1 Diabetes	NCT06239636	Phase I; Open label; Single-center	2	30–45	March 2024	June 2025
VCTX-211	An Open-Label, FIH Study Evaluating the Safety, Tolerability, and Efficacy of VCTX211 Combination Product in Subjects With T1D	NCT05565248	Phase I/2; Open label; Multicenter	40	18–65	January 2023	August 2025
VX264	A Phase 1/2 Study to Evaluate the Safety, Tolerability, and Efficacy of VX-264 in Subjects With Type 1 Diabetes Mellitus	NCT05791201	Phase I/2; Open label; Multicenter	17	18–65	May 2023	May 2026
VX880	A Phase 1/2/3 Study to Evaluate the Safety, Tolerability, and Efficacy of VX-880 in Subjects Who Have Type 1 Diabetes Mellitus With Impaired Hypoglycemic Awareness and Severe Hypoglycemia	NCT04786262	Phase 3; Open label; Multicenter	52	18–65	March 2021	June 2030

safety and possible delay of decline in C-peptide [44,48,49]. A variation on this process is synthetic peptides, specifically Imotopes™ (Imcyse) which are linear synthetic peptides representing an MHC/HLA class II-restricted T-cell epitope sequence linked to a thiol-disulfide oxidoreductase motif and have been shown to generate antigen-specific cytolytic $CD4^+$ T cells with effector memory phenotype and the ability to eliminate antigen-presenting cells that present this epitope with stability though not improvement in C-peptide [48]. Delivery methods have included antigen-specific plasmid vaccine approaches, intralymphatic delivery, and coadministration with alum, and intradermal microneedle delivery systems [50,51].

An altered human heat-shock protein 60 (DiaPep277) showed promise in preclinical studies and phase II trials in inhibiting destruction of β-cells and preserving insulin by inducing anti-inflammatory T-cells and activating regulatory T-cells by interacting with their Toll-like receptor 2 which diverts the immune response toward preservation of β-cells [52–63]. DiaPep277 reached a Phase III trial but while the extension study was underway, allegations of research misconduct by employees of Andromeda Biotech, Ltd., funder of the studies, led to Hyperion Therapeutics, Inc. which had by that time acquired Andromeda, to terminate further development [61].

Tolerogenic dendritic cells have also been of great interest due to their plasticity in acquiring immunoregulatory properties as they are responsible for presenting specific antigens which are critical in directing T-cell activation and display the ability to expand Treg cells which can then be transferred to patients to decrease autoimmunity. Multiple early phase trials have been conducted which have shown safety and positive immunomodulation with increased antigen-specific T regulatory cells and inhibited antigen-specific proinflammatory T-cells [64–66]. Clinical efficacy remains to be seen as the trial investigating pro-insulin peptide loaded tolerogenic dendritic cells, though without major adverse effects, did not show a significant change in C-peptide from baseline with the caveat of the study population comprising long-standing T1DM patients [66].

4. Stem cell transplantation therapy

Stem cells, with the ability to give rise to essentially any type of tissue or organ, have been looked at for use in T1D in another cell-based approach to target pancreatic islet regeneration and protection but also to modulate the immune response with inhibition of autoreactive T cells and reestablish peripheral tolerance of β cells.

Mesenchymal stem cells have been shown to have a variety of regulatory effects on the immune system including suppression of type 1 helper T cell development, promotion of the expression of active TGF-β1, and helping regulate adaptive Immunity [67]. Very small pilot clinical studies have shown safety of transplantation of umbilical cord derived mesenchymal stem cells delivered intravenously or through liver puncture but equivocal clinical outcomes in terms of variable levels of fasting and post-prandial C-peptide, though a few patients in the intervention arm were able to achieve insulin independence for 3–12 months [68,69].

One of the more aggressive interventions attempted to date is autologous nonmyeloablative hematopoietic stem cell transplantation to try to induce tolerance to pancreatic B cells. Several trials did have encouraging results with high rates of insulin independence though not durable, but the resource-intensiveness and transplant-related adverse effects limit broader adoption [70–73].

5. Exogenous regulatory T-cell (Tregs) therapy

Alterations in Foxp3+ regulatory T cells have been identified as a major immunological disturbance in T1D in genome-wide association and transcriptional studies [74]. Small pilot studies have investigated the safety of infusing autologous polyclonal Tregs, expanded in vitro to boost their numbers but in a phase 2 trial of a single dose of exapnded Tregs in children with new-onset T1D C-peptide was not preserved [75]. Another trial in which selective B cell depletion with rituximab was combined with Treg treatment resulted in significant increase in PD-1 receptor (+) CD4 +Treg, CD4 + effector T cells, and CD8 +T cell percentages with decreased insulin requirements though not insulin independence [76].

6. Anti-CD3 therapies

Most of the genetic loci most strongly associated with T1D involve T cell activation and antigen specificity like the interleukin-2 receptor (IL-2 R), human leukocyte antigen (HLA) complex, and cytotoxic T-lymphocyte – associated protein 4 (CTLA-4). As such there has been significant interest in interventions targeting the activation of T cells. One of the most promising avenues has been through targeting CD3 with anti-CD3 monoclonal antibodies. Several mechanisms have been postulated including direct inactivation of T cells, inhibition of apoptosis induction and induction of apoptosis or anergy of activated T cells [77–79].

Otelixizumab, an anti-CD3 monoclonal antibody with limited Fc receptor binding, has demonstrated benefit on preservation of β cell function at higher doses but has been hampered by adverse effects like cytokine release syndrome, Epstein-Barr virus reactivation and cytomegalovirus infection in most patients [80–83]. At lower doses it failed to show a significant difference in C-peptide levels or glycosylated hemoglobin A1c [84,85]

Teplizumab, a humanized Fc receptor – nonbinding anti-CD3 monoclonal antibody with high affinity to the ε chain of CD3, was approved by the FDA in 2022 to delay progression to stage 3 T1D in adults and children age ≥8 years with stage 2 disease [86]. This was particularly unique as the first agent approved to delay onset of an autoimmune disease. The approval was based on preclinical studies and several clinical trials of patients at both stage 2 and stage 3 of T1D [87–91]. Preclinical data showed that partial agonism by teplizumab led to effects on $CD8^+$ T cells integral to autoimmune-mediated destruction of pancreatic β-cells and did not require continuous administration [92]. The clinical trials showed that one course of teplizumab preserved C-peptide levels and was associated with lower insulin requirements and hemoglobin A1c (HbA1c) levels for at least 24 months [88] and up to 5

years in the extension studies with increases in partially exhausted memory KLRG1^{+}TIGIT^{+}CD8^{+} T cells and reduced secretion of IFNγ and TNFα [93].

Like many of the other immunotherapies, timing of intervention with teplizumab in terms of stage and β-cell reserve when treatment is initiated also affected outcomes, a with treatment soon after or before diagnosis at stage 3 the most effective; younger patients also had better C-peptide response though it was effective across all age groups [90,94,95]. There has been some conflicting data in recent-onset T1DM with phase II trials demonstrating some improvements in beta cell function that was not replicated in phase III trials but a pooled analysis of existing evidence suggested that anti-CD3 mAb treatment may still offer benefits over placebo with improved C-peptide response after stimulation [79].

Adverse effects of teplizumab thus far appear to be relatively mild and include self-limited lymphopenia, rash, GI symptoms [96]. Some have raised the concern about risk of additional type 1 T helper (Th1) mediated autoimmune conditions which have been associated with longer duration of clinical remission but further study is needed [97].

7. Costimulation blockade

Alternative strategies of affecting pathologic T cell functions have employed interference of the co-stimulation process which is the antigen-specific signal through the T cell receptor (TCR) and simultaneous antigen nonspecific signaling through a co-stimulatory receptor.

The interaction between CD80/86 on the antigen producing cells (APCs) and CD28 on the T-lymphocytes after the first interaction of the antigen in the groove of the major histocompatibility complex (MHC) molecule on APCs with TCR has been identified as a potential therapeutic target. Abatacept is a recombinant fusion CTLA4 protein that selectively binds to CD80/86 and blocks the interaction with CD28 leading to interference with the early phases of T-lymphocyte activation, proliferation, and survival [98]. In preclinical data, co-stimulatory blockade prevented diabetes in NOD mice only when administered in the stage between the development of insulitis but before the onset of frank diabetes [99]. A phase II trial of abatacept showed an attenuated reduction in β-cell function and lower A1c levels over 2 years, but despite continued administration of abatacept, decrease in β-cell function with abatacept was parallel to that with placebo after 6 months of treatment with an estimated 9.5 months' delay in the extension study [100,101].

Another agent interfering with co-stimulation that has been studied in T1D is alefacept, a lymphocyte function – associated antigen 3–Ig fusion protein that binds the costimulatory molecule CD2 on memory T cells and NK cells which disrupts the CD58-mediated costimulation of T cells and selectively depletes memory and effector T cells via NK-mediated antibody-mediated cytotoxicity [102]. In the phase II trial of alefacept, there was a variable response with only 30% of treated individuals showing significant preservation of endogenous insulin production (deemed responders) after 2 years compared with placebo-treated participants but significantly reduced exogenous insulin requirements and risk of major hypoglycemic events with sustained effect over 1 year after cessation of therapy [103,104]. In the responders, alefacept depleted CD4^{+} effector memory and central memory T cells while preserving regulatory T cells (Tregs), and preservation of insulin C-peptide was associated with the development of two CD8^{+} memory T cell populations with exhaustion-like features [105]. Higher frequency of anti-inflammatory CD4^{+}CD25^{+}CD127^{hi} T cells at diagnosis and higher frequency of proinflammatory islet autoreactive CD4^{+} T cells at baseline had a greater decline in C-peptide with alefacept treatment positively correlated with a favorable response to alefacept [106].

8. B-cell targeted immunotherapy

Exploration of the B lymphocyte contribution to primarily T-lymphocyte-driven diseases like T1D has yielded interest in the use of the anti-CD20 monoclonal antibody rituximab to selectively deplete B lymphocytes with preclinical data in NOD mice showing inhibition of the disease by this mechanism [107,108]. B lymphocytes can serve as key antigen-presenting cells that regulate peripheral T cell tolerance to islet β cells. It may not be essential though as there is a report of type 1 diabetes in a child with X-linked agammaglobulinemia, disorder of B-lymphocyte deficiency [109].

Two clinical trials of rituximab showed partial preservation of β cell function over 12 months with slower decline in C-peptide levels, lower HbA1c, and lower insulin requirement associated with increased T cell proliferative responses to diabetes antigens and attenuated β cell loss [110,111]. Adverse events were mostly grade 1 or grade 2, including fever, rash, and pruritus, worse after the first infusion and minimal with subsequent infusions without an increase in infections or neutropenia [110].

9. Cytokine therapies

Cytokines are important mediators of the complex interactions between the immune system and pancreatic β cells in the pathogenesis of T1D. Inflammatory cytokines such as TNF, IL-6 and IL-1 are thought to contribute to the development of T1D while regulatory cytokines like IL-33 and TGF-ß may prevent β cell destruction with restored immune tolerance.

Tumor necrosis factor-α (TNF-α) is a cytokine that has been implicated in autoimmunity leading to pancreatic damage [112]. Etanercept is a recombinant soluble TNF-α receptor fusion protein that binds to TNF-α and clears it from circulation. Small pilot studies have shown etanercept treatment both alone and in combination with rhGAD65/alum were safe, possibly associated with improved C-peptide levels in patients with recently diagnosed type 1 diabetes [113,114].

Interest has also turned to inhibitors of IL-1 which include anakinra and canakinumab as interleukin-1β has been shown to have direct β-cell proapoptotic action and mediate β-cell glucotoxicity [115]. Single agent therapy with anakinra and canakinumab in recent-onset diabetes was safe but not efficacious [116] though transcriptional analysis detected immunomodulation associated with treatment [117]. Interestingly, in other studies anakinra treatment has led to improvement in

insulin sensitivity, glycemic profiles and insulin requirements so it may be more effective when there is concomitant insulin resistance [118,119].

Interleukin-2 (IL-2) is an essential molecule in the expansion and function of the CD4 $^{+}$ FOXP3 $^{+}$ T regulatory (Tregs) cells that prevent autoimmunity, including that induced by anti-β-cell T effector cells (Teffs) [120]. Aldesleukin is a commercially available IL-2 produced by recombinant DNA technology and has been used in several phase I and II trials in type 1 diabetes. The first was in 2013 using low dose IL-2 and showed therapy was well tolerated with mild injection site reaction common, without any negative effect on glucose metabolism, and upregulated CD25 and FOXP3 on Tregs but not on CD4 $^{+}$ memory Teffs, and selectively induced pSTAT5 signaling in Tregs [121]. Further trials have focused on dose finding to sustain increased Treg responses without increasing Teff frequencies with higher doses being accelerating disease in NOD mice [122,123]. Clinical outcomes were equivocal with variable responses potentially related to baseline Treg proportions in CD4+ cells [124].

IL-6 receptor blockade has also been studied as a potential target as IL-6 augments the development of pathogenic Th17 effector cells and blocks the development and function of suppressive Tregs [125]. However, IL-6 receptor blockade with tocilizumab was not effective in modulating CD4+ T cell phenotypes nor did it slow the decline of β cell function in recent-onset type 1 diabetes [126].

As an alternative to the direct cytokine- and cytokine receptor-based therapies, Janus kinase (JAK) inhibitors, including baricitinib, have been studied due to the ability to suppress intracellular signaling by cytokines and have been effective disease-modifying treatments for other autoimmune diseases like rheumatoid arthritis. In T1D, JAK inhibitors impair cytokine-mediated MHC class I expression in islet cell cultures and prevent the destruction of β-cells by blocking CD8+ T cell activation and interaction with β cells [127]. A phase II trial of daily treatment with baricitinib over 48 weeks preserved the stimulated mean C-peptide level and was associated with less glycemic variability on continuous glucose monitoring data, though insulin requirements were not significantly different [128]. Two other JAK inhibitors, abrocitinib and ritlecitinib, are currently also under investigation in early-stage clinical trials.

Verapamil, a calcium channel blocker, has been the subject of interest with short-term beneficial effects in a small phase 2 trial with improved endogenous beta cell function, lower insulin requirements, and fewer hypoglycemic events [129]. The mechanism is postulated to be regulation of the thioredoxin system and promotion of an anti-oxidative and immunomodulatory gene expression profile in human islets with normalization of proinflammatory IL-21 levels and T-follicular-helper cell markers [130].

10. Stem cell transplantation therapy

Stem cells are undifferentiated cells able to give rise to essentially any type of tissue or organ and use in T1D has been targeted toward pancreatic islet regeneration and protection but also to modulate the immune response with inhibition of autoreactive T cells and reestablish peripheral tolerance of β cells.

Mesenchymal stem cells have been shown to have a variety of regulatory effects on the immune system including suppression of type 1 helper T cell development, promotion of the expression of active TGF-β1, and helping regulate adaptive immunity [67]. Very small pilot clinical studies have shown safety of transplantation of umbilical cord derived mesenchymal stem cells delivered intravenously or through liver puncture but equivocal clinical outcomes in terms of variable levels of fasting and post-prandial C-peptide though a few patients in the intervention arm were able to achieve insulin independence for 3–12 months [68,69].

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11. Future perspectives

There is a vast body of work on therapeutic targets within the immune system for the prevention and treatment of T1D that continues to grow with each passing year (Table 1). The FDA approval of teplizumab-mzwv (Tzield) in 2022 for delaying onset of stage 3 T1D marks a major landmark as the first approved therapy addressing the autoimmunity underlying T1D. While a therapy proven to delay onset of disease is certainly valuable, the ultimate goal remains complete prevention or reversal of the disease process. Thus far, many of the immunomodulatory approaches discussed in this review have not shown clinical efficacy or have some degree of efficacy limited by adverse effects or are limited to specific subpopulations of patients. Long-term durable improvements in glycemic control and restoration of insulin independence remain elusive. Despite this, the knowledge gained from this body of work shows more generally that an immunomodulatory approach to T1DM remains viable and there are several active clinical investigations in areas like regulatory T cell therapy, JAK inhibition, and IL-2 therapy.

Pancreas and islet transplantation with the goal of islet replacement have been viable therapeutic options for decades at this point, but require long-term immunosuppression and are limited by the pool of donor organs. For these reasons and concerns about long-term outcomes as well as recent major advances in diabetes technology and insulin delivery systems the number of pancreas transplants in the United States have declined significantly over the past decade [131]. Stem cell-derived pancreatic islet cells as in the VX-880 preparation (Vertex Pharmaceuticals Incorporated) offer a promising alternative obviating the need for donor organs but still require the use of immunosuppressants [132]. However, an intriguing development is Vertex's investigational VX-264 device, which encapsulates their stem cell-derived islet cells in a channel array surgically implanted in the abdominal wall to shield the cells from the immune system and avoid the need for immunosuppression [133]. A number of immunomodulators

including etanercept are also under investigation to prevent islet transplant rejection and graft failure [134].

Future areas of study still in the preclinical arena include the use of regulatory antigen-specific chimeric antigen receptor (CAR) T cells and genetically engineered macrophage cells generating extracellular vesicles that overexpress PD-L1 and Gal-9 to restrict islet autoreactive T lymphocytes. CAR T cell therapy is of particular interest to target the auto-reactive T cells driving the autoimmunity of T1DM and has achieved promising results in the non-obese diabetic mouse models of diabetes [135].

More work will need to be done in terms of how and who to screen for stage 1 diabetes and biomarkers like HLA that will allow identification of responders in a precision medicine approach to therapy.

Disclosure statement

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