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ABOUT COVER

Peer Review of *World Journal of Diabetes*, Tao-Hsin Tung, PhD, Researcher, Director, Epidemiologist, Evidence-based Medicine Center, Taizhou Hospital of Zhejiang Province Affiliated to Wenzhou Medical University, Taizhou 317000, Zhejiang Province, China. dongdx@enzemed.com .

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EDITORIAL

Immunotherapy in type 1 diabetes: Novel pathway to the future ahead

Sayantan Ray, Rajan Palui

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Sayantan Ray, Department of Endocrinology, All India Institute of Medical Sciences, Bhubaneswar 751019, India

Rajan Palui, Department of Endocrinology, The Mission Hospital, Durgapur 713212, India

Corresponding author: Rajan Palui, MBBS, MD, DM, Associate Specialist, Department of Endocrinology, The Mission Hospital, Bidhannagar, Durgapur 713212, India.
rajanpalui@gmail.com

Abstract

Since the discovery of insulin over 100 years ago, the focus of research in the management of type 1 diabetes (T1D) has centered around glycemic control and management of complications rather than the prevention of autoimmune destruction of pancreatic β cells. Fortunately, in recent years, there has been significant advancement in immune-targeted pharmacotherapy to halt the natural progression of T1D. The immune-targeted intervention aims to alter the underlying pathogenesis of T1D by targeting different aspects of the immune system. The immunotherapy can either antagonize the immune mediators like T cells, B cells or cytokines (antibody-based therapy), or reinduce self-tolerance to pancreatic β cells (antigen-based therapy) or stem-cell treatment. Recently, the US Food and Drug Administration approved the first immunotherapy teplizumab to be used only in stage 2 of T1D. However, the window of opportunity to practically implement this approved molecule in the selected target population is limited. In this Editorial, we briefly discuss the various promising recent developments in the field of immunotherapy research in T1D. However, further studies of these newer therapeutic agents are needed to explore their true potential for prevention or cure of T1D.

Key Words: Type 1 diabetes; Immunotherapy; Teplizumab; Antigen based therapy; Stem cell immunotherapy

Core tip: There has been a paradigm shift in research on type 1 diabetes (T1D) in the last decade. From managing the consequences of β cell death to prevention of β cell destruction, immunotherapy is showing the path forward. Recent regulatory approval of teplizumab in stage 2 of T1D marks the first significant advance in research of immunotherapy. In this Editorial, we briefly explore the recent developments and prospects in the field of immunotherapy in T1D encompassing antibody-based therapy, antigen-based therapy, and stem-cell-based immunotherapy.

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INTRODUCTION

The basic pathophysiology behind the development of type 1 diabetes (T1D) is immune-mediated destruction of insulin-producing pancreatic β cells[1]. The insulin-producing capacity of the endocrine pancreas depends upon its functional β cell number and size, collectively known as β cell mass. The body's aberrant immune system attacks and self-destroys the normal host tissue in autoimmune disease. Like any other autoimmune disease, progressive immune-mediated destruction of pancreatic β cells leads to a reduction of functional β cell mass in T1D. Once this β cell mass falls below the critical level, the onset of T1D ensues. However, the treatment of T1D primarily focuses on the exogenous replacement of insulin. Recently, studies have focused on exploring the possibilities of immune modulating therapy in T1D to protect pancreatic β cell mass from autoimmune destruction. Various molecules targeting mediators like T cells, B cells, cytokines and antigen-based therapies are now being evaluated to prevent or delay β cell destruction in T1D. Initial results in a few studies were encouraging in maintaining β cell function (as measured by c-peptide level) when used in the early stages of disease development[2]. In this Editorial, we briefly explore the potential of these novel immunomodulatory therapies in managing patients with T1D.

IMMUNOTHERAPY IN T1D

The pathophysiological stages of development of T1D are now being classified into three distinct stages: stage 1-positive antibody status with normoglycemia; stage 2-positive antibody status with dysglycemia or prediabetes; and stage 3-positive antibody status with frank diabetes or overt hyperglycemia[3]. Stage 3 of T1D development marks the onset of significant destruction of β cells. Stage 3 of disease development has been further subclassified into: stage 3a (not insulin requiring); stage 3b (insulin-requiring but with residual clinically relevant β cell mass); and stage 3c (insulin requiring without any clinically relevant β cell mass)[4]. The immune system plays a pivotal role in the de-velopment of T1D. Although it was classically thought that autoimmune destruction of β cells is mainly due to T cells, B cells also play a critical role[5]. Once self-tolerance is lost, and with subsequent environmental triggers, autoreactive T cells are developed. When the self-antigens from β cells are presented by antigen-presenting cells (APCs) to these autoreactive T cells, cytotoxic T cells are activated, destroying pancreatic β cells. The main target of immunotherapy in T1D is to either prevent or at least delay the immune-mediated destruction of β cells[6,7]. The immunotherapy in T1D can be either-antibody-based therapy, antigen-based therapy, or stem cell therapy. In the following sections, we will briefly discuss the recent status of immunotherapy in T1D.

ANTIBODY-BASED IMMUNOTHERAPY

Antibody-based therapies against different target antigens have been tried to halt the autoimmune destruction of pancreatic β cells. These antibody-based therapies (monoclonal and polyclonal) are directed mainly against T cells or B cells or cytokine signaling (Figure 1). Most of these studies that evaluated antibody-based immunotherapies in T1D were done in stage 2 or early stage 3 of T1D. The details of the important antibody-based immunotherapies are given in the next section.

T-cell-directed antibody therapy

Teplizumab: Teplizumab is a humanized monoclonal antibody [immunoglobulin G (IgG) 1 kappa] directed against the CD3 portion of T-cell receptors[8]. This molecule is non-Fc binding, thus reducing the risk of cytokine release syndrome (CRS) compared to previous generations of anti-CD3 molecules. Teplizumab produces early suppression of cellular immune response by preventing the binding of $CD4^+$ T helper cells to APCs by inhibiting CD3 of T-cell receptors. Prolonged and sustained binding of this molecule exerts a state of $CD8^+$ T-cell exhaustion and thus induces chronic immunosuppression[9]. In 2022, teplizumab obtained US Food and Drug Administration (FDA) approval for delaying or prevention the onset of stage 3 of T1D in patients currently in stage 2 of T1D. It was approved for use in adults and

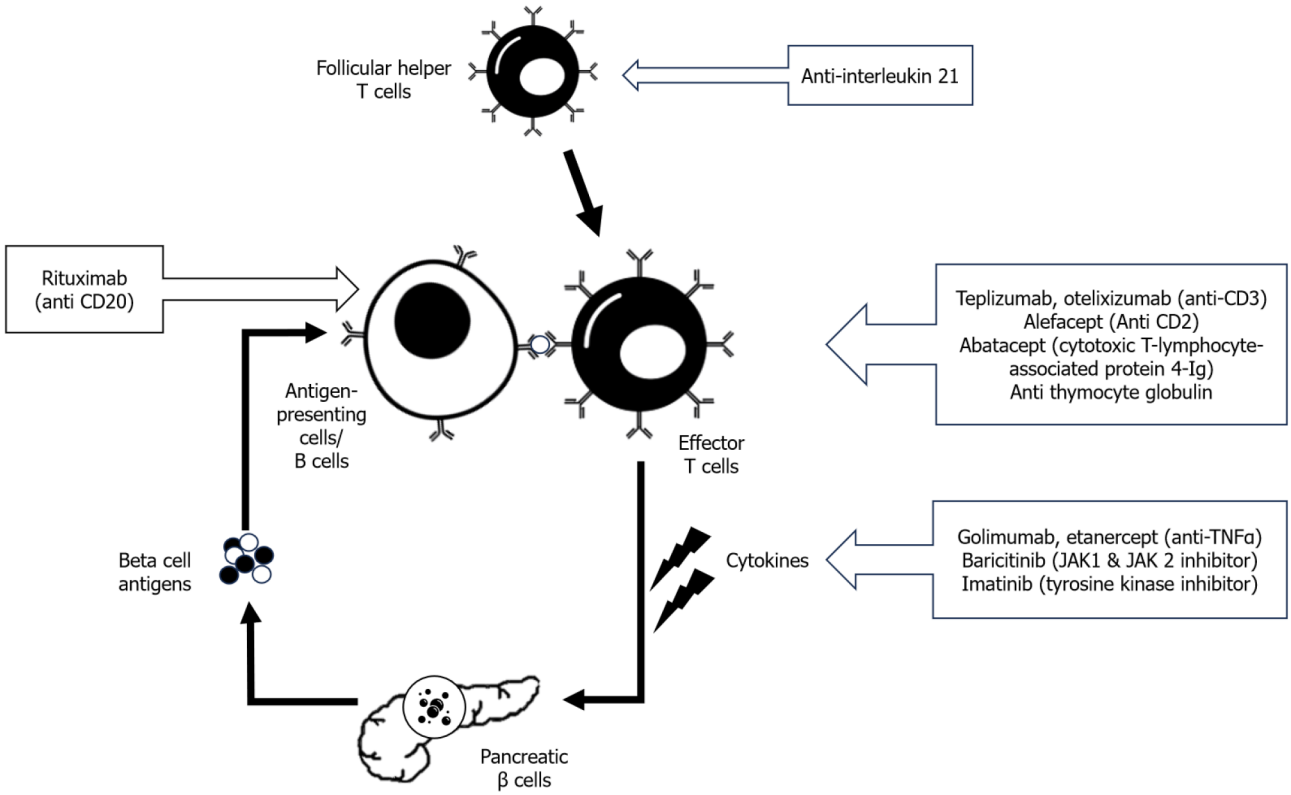

Figure 1 Outline of antibody-based immunotherapy in type 1 diabetes.

children aged > 8 years[10].

The landmark trials that evaluated the safety and efficacy of teplizumab are summarized in Table 1[11-15]. All of these studies are done in stage 3 of the T1D except the TrialNet study, which was done in stage 2 of T1D[12]. These trials showed a more favorable c-peptide response in teplizumab than in the placebo arm. In the meta-analysis by Kamrul-Hasan *et al*[16], 834 subjects from six studies that evaluated the efficacy and safety of teplizumab as a disease-modifying therapy in T1D, were included. The authors reported greater preservation of area under the curve (AUC) of c-peptide in the teplizumab arm through 6-24 mo of follow-up [mean difference 0.07 nmol/L (95% confidence interval: 0.01-0.14, P = 0.03)]. Moreover, fewer patients reported reduced c-peptide response after 2 years of follow-up in the teplizumab arm (odds ratio 0.12). However, the authors also reported an increased risk of grade 3 or higher adverse events, nausea, rash, lymphopenia, and discontinuation of the study drug in the teplizumab arm than placebo. Adverse events are commonly associated with any monoclonal-antibody-based therapy. In the case of teplizumab, most adverse drug reactions occurred during the treatment period and were mild to moderate and manageable. Similarly, other recent meta-analyses also reported that patients in the teplizumab arm had higher AUC of c-peptide and lower exogenous insulin requirement but similar glycosylated hemoglobin (HbA1c) levels in comparison to placebo[17,18]. In another meta-analysis, Liu *et al*[19] included both the anti-CD3 monoclonal antibodies, teplizumab (seven studies) and otelixizumab (five studies). The authors also reported greater AUC of c-peptide and decreased exogenous insulin requirement in the anti-CD3 antibody arm. They found no significant difference in HbA1c and serious adverse events between the study and placebo arm[19]. Moreover, in the follow-up study of the AbATE trial, prolonged immunological response was reported even after 7 years of diagnosis of T1D in patients who initially responded to teplizumab[20].

Predictors of therapeutic response: The studies done with teplizumab also tried to find out possible predictors of response to therapy. If we can establish predictors for therapeutic response for this expensive therapy, it can be used cost-effectively in selective patients who are more likely to respond. The authors of the Protégé Trial reported that the recently diagnosed patients (< 6 wk) had the highest response. Moreover, patients living in the USA, patients with lower HbA1c, higher c-peptide, and lower insulin requirement at baseline were more likely to respond[14]. As younger patients exhibit stronger immune reactions than adult patients, they have a higher chance to respond[14,15]. Better glycemic control as measured by lower HbA1c level was also reported as a favorable predictor in trials done in stage 3 T1D[15,21]. This may be due to higher preserved β cell mass or increased insulin sensitivity in the treatment responders. The relationship of treatment outcome with baseline β cell reserve as measured by AUC of c-peptide is heterogeneous and may be related to the stage of T1D. Patients in stage 2 T1D are likely to respond when the baseline c-peptide level is lower, whereas a higher baseline c-peptide is a response predictor for patients in early stage 3 disease[12,14,21]. This paradoxical finding can be explained by the hypothesis that prior to significant immune mediated destruction in early stage of disease (stage 2), patients with stronger immune reaction are more likely to respond to immunomodulatory therapy. On the contrary, in patients with a later stage of disease (stage 3), when immune-mediated destruction is already significant, patients with higher residual functioning β cell mass respond better to therapy. The TrialNet study group also reported that patients

Table 1 Major studies evaluating the efficacy and safety of teplizumab

Ref.	Study design	Intervention	Population	Major outcome
Ramos *et al* [11], 2023	PROTECT study	Phase 3, randomized, placebo-controlled trial with teplizumab or placebo for two 12-day courses	The 328 participants, stage 3 T1D, age 8-17 years, within 6 weeks of diagnosis	Higher stimulated c-peptide levels (teplizumab *vs* placebo) (least squares mean difference, 0.13 pmol per mL; 95%CI: 0.09-0.17; $P < 0.001$); no significant difference in HbA1c level, insulin requirement or hypoglycemia; ADR: headache, gastrointestinal symptoms, rash, lymphopenia, and mild cytokine release syndrome
Herold *et al* [12], 2019	TrialNet study	Phase 2, randomized, placebo-controlled, double-blind trial of teplizumab (single 14-day course)	The 76 participants, relatives of T1D, stage 2, age > 8 years	Low-risk diagnosis of T1D (teplizumab *vs* placebo) (hazard ratio 0.41; 95%CI: 0.22-0.78; $P = 0.006$); longer median time to diagnose T1D (teplizumab *vs* placebo) (48.4 months *vs* 24.4 months); ADR of lymphopenia and rash
Herold *et al* [13], 2013	AbATE Study	An open-label, randomized, controlled trial with teplizumab (two of 14-day course, one year apart)	The 83 participants, stage 3 T1D, age 8-30 years, within 8 weeks of diagnosis	Reduced decline in c-peptide at 2 years (-0.28 nmol/L; 95%CI: 0.36-0.20) *vs* control (-0.46 nmol/L; 95%CI: 0.57-0.35; $P = 0.002$); ADR: Rash, transient upper respiratory infections, headache, and nausea
Hagopian *et al*[14], 2013	Protégé study	Phase 3, randomized, double-blind, parallel, placebo-controlled 2-years with teplizumab (3 dosing regimens, two of 14 days course, 26 weeks apart)	The 462 of 516 participants completed 2 years follow up, stage 3 T1D, age 8-35 years, within 12 weeks of diagnosis	Reduced the loss of area under curve mean c-peptide at 2 years (teplizumab *vs* placebo) ($P = 0.027$); ADR: lymphopenia; no differences in adverse events or serious adverse events among groups at 2 years
Herold *et al* [15], 2013		Randomized placebo-controlled trial	The 63 participants, stage 3 T1D, within 4-12 months of diagnosis	The 21.7% higher c-peptide response (teplizumab *vs* placebo) [0.45 *vs* 0.371; difference, 0.059 nmol/L (95%CI: 0.006-0.115 nmol/L)] ($P = 0.03$); the teplizumab group required less exogenous insulin ($P < 0.001$) with no significant difference in HbA1c level; ADR: rash, lymphopenia and nausea

ADR: Adverse drug reaction; CI: Confidence interval; HbA1c: Glycosylated hemoglobin; T1D: Type 1 diabetes.

who were anti-zinc transporter 8 (ZnT8) antibody negative, HLA-DR3 negative, and HLA-DR4 positive responded better to teplizumab than placebo[12]. Increased CD8+ T cell (cytotoxic and memory) and decreased $CD4^+$ T cell (helper and memory) cells were observed in treatment responders in different trials[12,13,15,22]. However, none of these metabolic or immunologic predictors were consistently reported across all the studies and thus needed further validation in future studies.

Cost-effectiveness: One of the significant limitations of the broader use of this novel molecule is its premium cost. Teplizumab costs around $193000 for a single course of 14 d therapy. Mital *et al*[23] tried to analyze the cost-effectiveness of teplizumab depending on the HLA-DR3, HLA-DR4, and ZnT8 antibody status. They predicted if the cost of therapy is more than $100000, treating only a quarter of the patients at risk will be cost-effective. If we consider current annual cost of management of T1D patients and cost of teplizumab therapy, it may be cost-effective only if the prospective patient fulfills all the favorable criteria of therapeutic response- HLA-DR3 negative, HLA-DR4 positive and negative anti ZnT8 antibody status[23,24]. However, cost cannot be the sole deciding factor for restricting the benefit of this drug to whom it can be effective. We hope that in future this drug will be more affordable for the larger number of T1D patients. Guidelines for practical clinical use, screening, and proper patient selection for this molecule are now being formulated [25].

Otelixizumab: Otelixizumab is another anti-CD3 monoclonal chimeric and humanized antibody that had been evaluated in T1D. In a dose-finding, safety, and tolerability assessment randomized control trial (RCT), a 6-d course of otelixizumab in four different dosages was given to 30 T1D patients within 32 d of diagnosis[26]. A sustained metabolic response of preserved c-peptide level was found for up to 18 mo following a 9 mg dose of otelixizumab. However, not all the studies showed significant improvement in c-peptide level when compared to placebo, specifically when it is used in lower dosage[27,28]. The presence of a positive insulin autoantibody is reported to be a predictor of therapeutic response[29].

Alefacept: Alefacept is a fusion protein that antagonizes CD2 costimulatory receptors, inhibiting T cell proliferation and action. In T1DAL RCT, two 12-d courses of alefacept were given at 12 wk apart in 49 newly diagnosed (< 100 d) T1D patients[30]. After 24 mo, patients in the alefacept arm showed significantly higher AUC for c-peptide response for 2 and 4 h ($P = 0.015$ and $P = 0.002$, respectively). There was also a significant reduction of exogenous insulin requirement and hypoglycemia event in the alefacept arm. Alefacept also induced favorable immunological response by depleting $CD4^+$ and $CD8^+$ T cells[30]. However, at 12 mo follow-up, there was no significant difference in c-peptide AUC compared to the placebo[31].

Abatacept: Abatacept is a fusion protein of the Fc portion of IgG1 and cytotoxic T-lymphocyte-associated antigen 4, which blocks the costimulatory signal by blocking the CD28 T-cell receptor. In a multicenter RCT, 112 newly diagnosed T1D patients (between 6 and 45 years of age) were included and intravenous abatacept was given for 27 infusions over 2

years. The authors reported significant preservation of β cell function as measured by higher AUC of c-peptide at 2 years of follow-up in patients who received abatacept (P = 0.0029)[32]. In the follow-up study, the authors also reported persistent beneficial effects in the abatacept arm even after 1 year of cessation of treatment (P = 0.046)[33]. However, in a phase 2 RCT where 101 participants of stage 1 T1D patients were included, monthly infusion of abatacept for one year failed to significantly delay the progression of T1D (P = 0.11)[34].

Antithymocyte globulin: Anti-thymocyte globulin (ATG) is a rabbit polyclonal IgG antibody that acts against multiple T-cell antigens. It may act through various mechanisms like T-cell depletion, induction of anergy in T cells, and selective induction of regulatory T (Treg) cells[35]. In the START trial, high-dose ATG (6.5 mg/kg) failed to show any significant preservation of c-peptide response in recent onset T1D patients[36]. ATG showed acute T-cell depletion sparing effector memory T cells. Higher adverse events, including CRS, were reported in the ATG arm. To decrease the risk of these adverse events, later studies used a lower dosage of ATG. In the TrialNet ATG-granulocyte colony-stimulating factor (G-CSF) study, low-dose ATG (2.5 mg/kg) or low-dose ATG with pegylated G-CSF were studied in recent onset (< 100 d) T1D patients[37]. The authors reported significant HbA1c reduction and slowing of c-peptide decline after 1 year of follow-up in the low-dose ATG group without any extra benefit with the addition of GCSF. In the 2-year follow-up of the same trial, although reduction in HbA1c and T-cell depletion with preservation of Treg cells were reported in both ATG as well as ATG with G-CSF arm, higher AUC of c-peptide in comparison to placebo was seen only in the low-dose ATG arm but not in the ATG with G-CSF arm[38]. However, low-dose ATG with GSF had been reported to preserve the AUC of c-peptide following mixed meal tolerance tests in other studies[39,40]. In a cost-effectiveness analysis study, low-dose ATG was found to be more cost-effective than other immunotherapies (including teplizumab) or no therapy in patients with recent onset T1D[41].

Anti-interleukin 21 and liraglutide: Researchers have also explored the role of combination therapy in immunomodulatory therapy for T1D. Anti-interleukin (IL)-21 antibody antagonizes IL-21-mediated autoreactive T-cell trafficking to pancreatic islets as well as proliferation of effector and follicular helper T cells[42,43]. Glucagon-like peptide-1 agonists like liraglutide have been reported to improve β cell survival[44,45]. In the proof of concept animal study in the T1D mouse model, Rydén *et al*[46] reported that the combined anti-IL-21 and liraglutide therapy can reverse diabetes. In a phase 2, multicenter, parallel-group, placebo-controlled RCT, 308 T1D patients were randomized to four arms – anti-IL-21 only, liraglutide only, combined anti-IL-21 with liraglutide, or placebo. The decline of post-mixed meal tolerance test c-peptide level at 52 wk was significantly smaller (P = 0.0017) in the combined group in comparison to the placebo, but not in the anti-IL-21 only (P = 0.093) or liraglutide only (P = 0.38) groups[47]. Although the authors also reported a reasonable safety profile for this combination therapy, it should be further confirmed in future phase 3 trials.

B-cell-directed antibody therapy

Rituximab: Like various T-cell depletion therapies, depletion of B cells using anti-CD20 monoclonal antibody rituximab has also been studied in T1D. In a placebo-controlled RCT (TrialNet Anti-CD20), 87 recently diagnosed T1D patients were randomized to four different dosage infusions of rituximab or placebo[48]. The patients in the rituximab arm showed significantly higher AUC of c-peptide than placebo during the mixed meal tolerance test at 1-year follow-up. The patients in rituximab also had lower HbA1c and required less exogenous insulin. Patients who responded to rituximab showed greater T-cell proliferative response to islet cell antigens[49]. However, at 30 mo follow-up of the same study, there was no significant difference in the AUC of c-peptide between the rituximab and placebo arms[50]. The effect on B-cell depletion by rituximab also weaned off by 18 mo. The authors concluded that although rituximab can delay the decline of c-peptide in T1D, it cannot prevent the inevitable β cell loss[50]. In a recent RCT, combined therapy of autologous CD4+ $CD25^{high}CD127^{-}$ Treg cells and rituximab was found to be superior in maintaining remission in recently diagnosed T1D patients in comparison to either the monotherapy or control[51].

Antibody therapy against cytokine signaling

Golimumab: The proinflammatory cytokine, tumor necrosis factor (TNF)-α plays an essential role in the pathogenesis of various autoimmune diseases[52]. In animal model studies, antagonizing TNF-α has been shown to prevent the development of autoimmune diabetes[53,54]. In the phase 2 T1GER study, the efficacy and safety of golimumab (anti TNF-α monoclonal antibody) were evaluated in recently diagnosed T1D patients (stage 3 of T1D)[55]. Patients were randomized to every fortnightly subcutaneous injection of golimumab (56 patients) or placebo (28 patients) for 52 wk. The authors reported higher 4-h mixed meal tolerance test AUC of c-peptide (0.64 pmol/mL *vs* 0.43 pmol/mL, P < 0.001) and lower exogenous insulin requirement (0.51 U/kg/day *vs* 0.69 U/kg/day) in golimumab arm than placebo. In the 2-year follow-up study (52 wk of therapy and 52 wk of off-therapy) of the same trial, patients in the golimumab arm showed persistently lower reductions in AUC of c- peptide at 78 and 104 wk compared to placebo[56]. The adverse events were reported to be similar in both arms of the study.

Etanercept: Etanercept, the recombinant soluble TNF-α receptor protein, blocks the activity of proinflammatory cytokine TNF-α and thus can be helpful in autoimmune diseases. In a pilot RCT, 18 patients with recently diagnosed T1D were given subcutaneous twice weekly etanercept or placebo for 24 wk[57]. The patients in the etanercept arm showed better HbA1C levels (5.9% *vs* 6.8%; P < 0.05) and AUC of c-peptide (+ 39% *vs* -20%; P < 0.05) than placebo, suggesting β cell preservation. In a recent study, etanercept was combined with glutamic acid decarboxylase (GAD-alum) and vitamin D (etanercept diamyd combination regimen) to evaluate the efficacy in newly diagnosed anti-GAD antibody-positive T1D patients[58]. However, this combination failed to show any significant beneficial effect in this trial.

Baricitinib: Baricitinib is a Janus kinase (JAK1 and JAK2) cytokine inhibitor which had been used successfully in autoimmune disorders[59,60]. In the phase 2 multicenter RCT (BANDIT study), 91 recently diagnosed T1D patients were randomized to either oral baricitinib (4 mg/d) or placebo for 48 wk[61]. Following the mixed meal tolerance test, the c-peptide level was significantly higher in the baricitinib group than placebo (P = 0.001) at 48 wk follow-up. Exogenous insulin requirement was also considerably low in the baricitinib group, with no significant difference in HbA1C level compared to the placebo. The adverse events were reported to be similar in both groups.

Imatinib: The role of small tyrosine kinase inhibitors like imatinib also had been evaluated in T1D. In a nonobese diabetic mouse study, imatinib had been reported to induce durable remission[62]. Imatinib has been postulated to act through both immunological and metabolic pathways involving endoplasmic reticulum stress in β cells[63]. In a phase 2 multicenter RCT, patients with recent onset T1D were randomized to receive either oral imatinib (400 mg/d) or placebo for 26 wk[64]. The patients in the imatinib arm showed higher AUC of c-peptide compared to the placebo at 12 mo (P = 0.048) follow-up. However, the effect was not sustainable at 24 mo. Future studies are needed to find the ideal dose and duration as well as to monitor the adverse effects of this exploratory therapy.

Apart from the pharmaceutical agents mentioned above, other molecules like verapamil, ladarixin, canakinumab and anakinra were also studied in recent onset T1D with variable success[65-67]. In a recent meta-analysis, which evaluated the effect of monoclonal antibody-based immunotherapy on c-peptide level in patients with recent onset T1D, 11 studies of four antibody-based immunotherapy (teplizumab, rituximab, otelixizumab and abatacept) were included[68]. The authors reported favorable c-peptide response in favor of β cell protection with all these four molecules. In a comparative study, the results (AUC of c-peptide response) from the primary studies of various immunotherapies (teplizumab, alefacept, abatacept, rituximab, high dose ATG, and low dose ATG ± G-CSF) in T1D were evaluated to rank them according to their effectiveness[69]. The authors reported that low-dose ATG and teplizumab showed maximum impact in preserving β cell function among the molecules studied. However, when these immunotherapies are used, we must be careful about the potential risk of adverse events like lymphopenia, viral infections, and CRS.

We should also remember that the sole FDA-approved immunotherapy, teplizumab, is indicated to be used only in stage 2 of T1D and thus practically has minimal application unless the disease is diagnosed early in the dysglycemia stage. More widespread screening programs like TrialNET, ASK, Sanford Population-Level Estimation of T1D Risk GEnes in Children, and T1 Detect JDRF are needed to find suitable candidates who are at the window of opportunity for this therapy[70]. The durability of the immunotherapies and frequency of dosage to maintain a state of disease remission should also be evaluated in longitudinal follow-up studies. Another concern is the safety of the long-term use of these immunomodulatory therapies due to the risk of CRS, reactivation of viral infections, *etc.* Thus, further well-designed RCTs with longer follow-up are needed to evaluate the efficacy, durability of therapeutic response, and safety of these immunotherapies in T1D. Moreover, the drugs should be affordable and cost-effective to ensure the access of newer therapies to the target populations.

ANTIGEN-BASED IMMUNOTHERAPY

Although several nonspecific approaches of immunoregulation have been trialed for T1D, antigen-based immunotherapy is thought to be a more favorable approach owing to its specificity and possible long-lived effects, without broad immunosuppression being needed[71]. The basis of antigen-specific immunotherapy is either inactivation of the pathogenic effector T (Teff) cells functionally, transforming them into Treg cells, or both. An ideal antigen-based immunotherapy could be administered multiple times (nonimmunogenic by itself) and would induce Treg cells that could repress islet-specific Teff cells of various specificities and lead to long-standing tolerance[72]. However, many questions are to be considered, along with the duration of the treatment and cost when designing antigen-specific immunotherapy.

Antigen targets and delivery strategies

For antigen-based immunotherapy to be fruitful, the subject getting treatment must have a T-cell population specific for the therapy-delivered antigen. Therefore, when developing an immunotherapy for individuals with T1D, the major specificities of circulating autoreactive T cells are essential factors to consider. In T1D individuals, the isolated $CD4^+$ and $CD8^+$ T-cell clones with specificity for a range of autoantigens have been identified. These include insulin, pre-proinsulin, GAD, islet antigen-2, islet glucose-6-phosphatase catalytic subunit related protein, and chromogranin A. Recently, proinsulin (c-peptide region) has been a hotspot for responsiveness of T cells in patients with T1D[73,74]. Furthermore, islet inflammation along with endoplasmic reticulum stress can cause further islet-derived antigen release, thereby inducing epitope spreading, post-translational modification of peptides, and fusion of peptide fragments originating from different proteins with subsequent generation of hybrid peptides[75]. Therefore, an in-depth knowledge of the critical antigenic targets and their kinetics during the progression of disease is crucial for choosing the most fitting targets for antigen-based therapy. Disease heterogeneity adds to the complexity of antigen-specific immunotherapy in T1D because of a subgroup of patients depending on their HLA alleles or disease endotypes[76]. Heterogeneity and HLA haplotype can influence the presentation of epitopes from islet antigens to the autoreactive T cells as well as the response of T cells [77,78]. Considerations and requirements for antigen-based immunotherapy in T1D are illustrated in Figure 2. Experts have used different delivery strategies for antigen-specific immunotherapy, for example, proteins and peptides, plasmid DNA, cell-based strategies, antigen-loaded nanoparticles, and liposome-based approaches (Table 2). The key question is which approach is more likely to restore β cell tolerance?

Table 2 Antigen-specific immunotherapies- strengths and weaknesses

Strategies	Immunological target	Advantages	Disadvantages
Autoantigenic peptides and proteins	APCs	Biocompatible; possibility to conjugate to a vehicle	Short half-life; adjuvant required
Autoantigen-encoding plasmid DNA	APCs	Long-lived effect	Gene therapy
Antigen-loaded cell-based strategies	Autoreactive T cells	Powerful immunoregulatory effect	Leukapheresis required; personalized medicine
Antigen-loaded nanoparticles and liposomes	APCs and T cells	Customizable; powerful immunoregulatory effect; might act by biomimicry	Synthetic; preclinical developmental phase

APCs: Antigen-presenting cells.

Preclinical and human studies

The antigen-specific approach involves the delivery of β cell autoantigens through a route and regimen that induces immune tolerance. Several antigen-specific approaches have entered into trials in the last decade to explore their safety, feasibility, and efficacy using different delivery strategies[79]. Recently completed and ongoing immunotherapy trials using antigen-specific strategies in T1D are reviewed elsewhere[80]. Single-peptide immunotherapy using a proinsulin sequence showed hints of efficacy and immunomodulation and was well tolerated[81]. Gibson *et al*[82] used a preclinical, humanized model of peptide immunotherapy. They showed that combining numerous different β cell peptides into a single injectable may produce a significantly increased effect compared with a single peptide in generating immune regulation. A recent study has addressed whether therapies delivering several antigens concurrently are efficacious and any safety issues that can arise from administration of multiple antigens. A mixture of six β cell peptides from two islet autoantigens was administered to patients with recent-onset T1D[83]. Multiple-peptide immunotherapy showed the potential to rectify immune regulatory defects central to the pathobiology of T1D in this first-in-human study. No serious adverse effects were observed in groups that received drug treatment. Together with the observations in pre-clinical models that delivery of multiple peptides from more than one antigen may have more impact than a monopeptide[82], these recent findings justify future well-designed clinical trials.

The last decade has seen the knowledge translated into definite antigen-based immunotherapies, promising to restore the breach of immunological tolerance to β cell autoantigens selectively. However, in both prevention and reversion trials in T1D, suboptimal effects have been obtained so far. Consequently, there is still a need to optimize those immunotherapies and their associated factors, such as patient and disease heterogeneity; choice of antigen (peptide or whole molecule, conventional or unconventional, single antigen or cocktail); posology; administration patterns, route, timing and use of adjuvants; biomarkers for stratification and therapeutic outcome[80].

STEM-CELL-BASED IMMUNOTHERAPY

T1D can be reversed by transplantation of pancreas or islet cells, which serves as proof of principle for cell-based therapy [84]. However, several issues limit its widespread use, particularly the insufficient supply of highly functional β cells. Yet, the sourcing problem could be circumvented by differentiating stem cells (SCs) into insulin-producing cells, and it has garnered the most enthusiasm for creating functional β cells[85,86]. These SC-derived islets could be derived from a single-cell source using a standardized process. The resulting cell product could be well characterized, allowing for more predictable transplant outcomes.

SCs [embryonic SCs (ESCs), induced pluripotent SCs (iPSCs)], and adult SCs are being widely explored for T1D therapeutics[87]. In preclinical studies, ESC-derived β cells have shown favorable results by insulin production in response to glucose stimulation and restoration of normoglycemia[87]. iPSCs offer a practical alternative to ESCs. They can be derived from adult somatic cells, thus eliminating ethical concerns. In diabetic mouse models, iPSC-derived β cells have also exhibited the ability to secrete insulin and restore normoglycemia. Besides iPSCs, adult SCs, including mesenchymal SCs and hematopoietic SCs, have been investigated for T1D as well[88].

Recent technological advances have made human clinical trials utilizing SC-derived pancreatic endoderm cells (PECs) possible. An initial 2014 human clinical trial used the ViaCyte Inc. device (VC-01) to immunoprotect the cells using a cell-impermeable membrane entirely. Although some endocrine cells were found, fibrosis around the capsule led to graft loss, and insulin secretion was not detected from the device[89,90]. To circumvent this issue, a clinical trial (NCT03163511) was initiated in 2017 to evaluate the newer PEC-Direct device (PEC-01 cells implanted subcutaneously in VC-02 devices) that contained membrane openings allowing vascularization to develop nutrient exchange and promote survival of cells. Total immunosuppression was required after transplantation. In 63% of units, insulin expression within β cells was observed at 3-12 mo post-transplantation, with a preponderance of α cells reflecting the immature graft state. The recently published reports from this ongoing trial demonstrated detectable levels of c-peptide in peripheral blood by 6-9 mo post-transplantation[91,92]. Vertex pharmaceuticals embarked on a clinical trial with T1D patients in 2021, where an ESC-

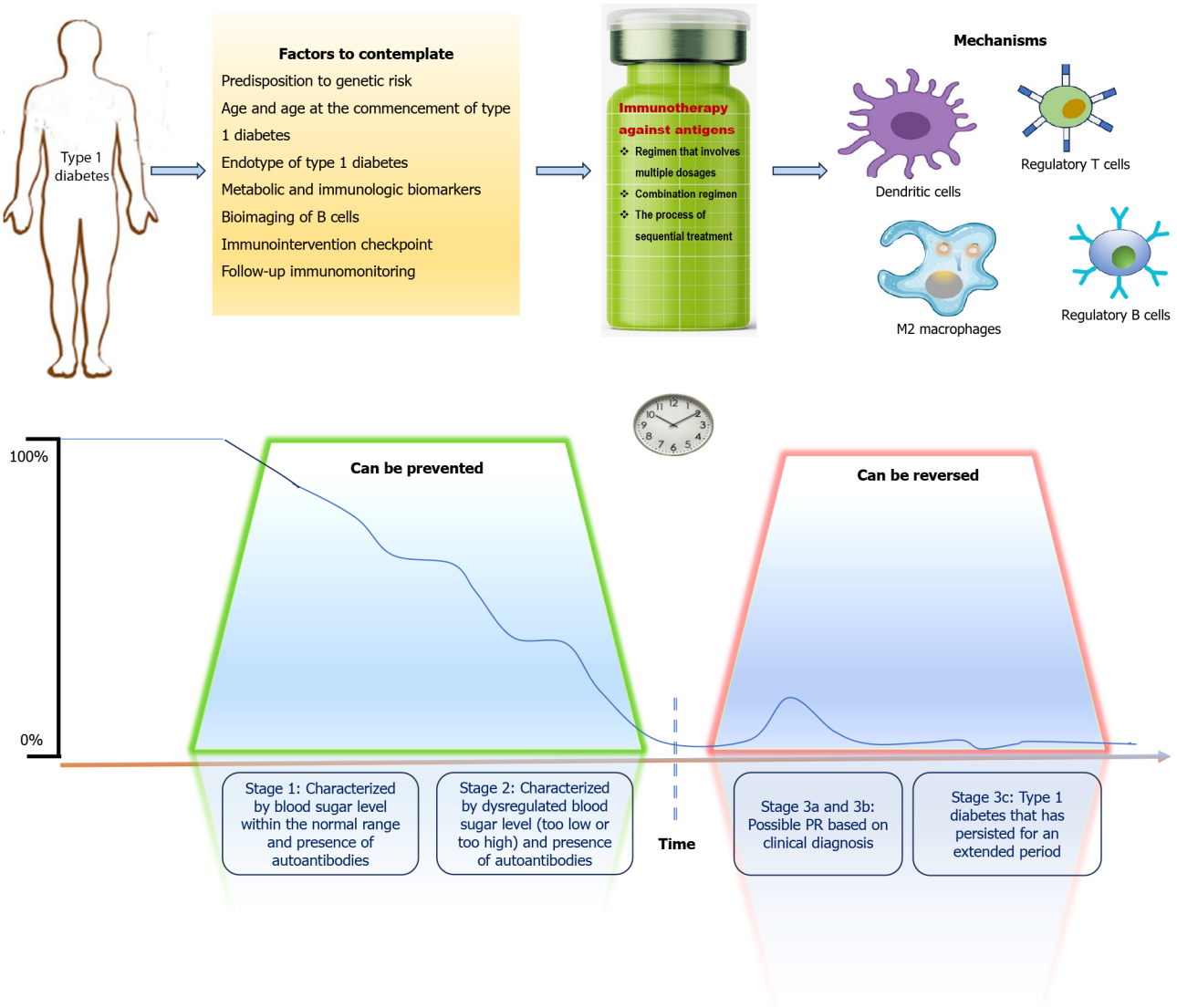

Figure 2 Considerations and requirements for successful immunotherapy using antigen-specific approaches in type 1 diabetes. If the antigen-specific therapy is administered before the clinical diagnosis of type 1 diabetes (T1D) (stage 1 and 2), the development of T1D could be revoked; otherwise, if T1D has already been diagnosed (stage 3), the intervention should be accompanied by a β cell regenerative agent to restore the β cell mass and its functionality. One should consider the genetic risk susceptibility of the patient, age and age at T1D onset, autoreactivity profile and T1D endotype, metabolic and immunologic biomarkers, and ideal antigen-specific therapy time point for the treatment to be as personalized as possible. On this basis, the partial remission (PR) – when β cell tolerance is thought to be restored transiently – and exploring subsequent but milder PR phases could be of value as immune intervention checkpoints (in stage 3a and 3b). In addition, the antigen-specific immunotherapy should enforce the generation of tolerogenic dendritic cells, M2 macrophages, regulatory T (Treg) cells and regulatory B cells, thus reeducating the immune response against β cell autoantigens and re-establishing β cell immunological tolerance.

derived islet, VX-880, was transplanted without an immunoprotective device under immunosuppressive coverage. Initial findings seem promising[93]. An ongoing Vertex trial (NCT04786262) will determine whether the success can be replicated and investigate the safety of implantation of SC-derived islets in a site such as the liver. In addition to these critical advances, several organizations intend to conduct clinical trials of functional SC-derived islets[94]. It is important to note that although freed from reliance on exogenous insulin, the Vertex result presently is based on a single patient and that ViaCyte's strategy, established on differentiation of PEC to adequate numbers of functional β cells within porous devices, has not yet been shown to work. The requirement for long-term immunosuppression may restrict the clinical application of both the ViaCyte and Vertex approaches.

As things stand, the clinical trial results highlight the great promise SC-islets hold for treating T1D. The last few years have been notable for game-changing early progress in clinical trials with SC-based therapies for T1D[95]. Nevertheless, several remaining challenges need to be addressed before this SC therapy can be converted into a routine procedure. The central pillars of a successful SC-islet therapy for T1D are illustrated in Figure 3.

CONCLUSION

T1D involves the autoimmune destruction of insulin-producing β cells in the pancreas. Over 100 years since the discovery

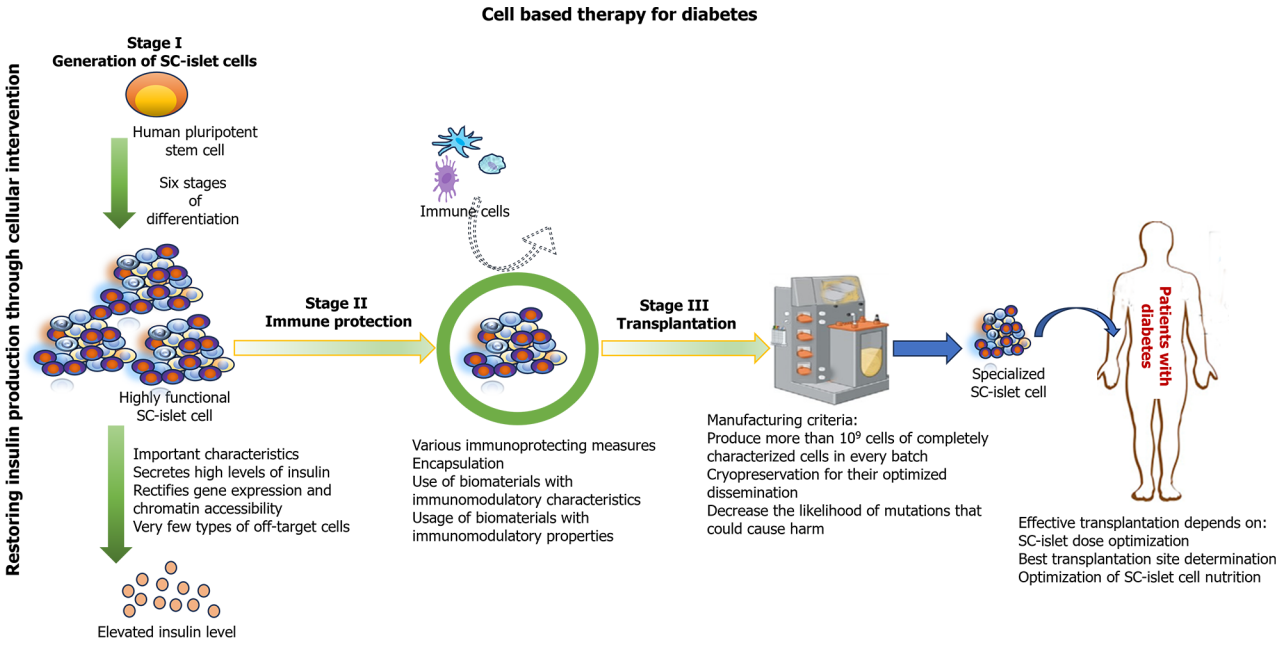

Figure 3 Key components of successful stem cell derived islet therapy for treating type 1 diabetes.

of insulin, there is still no cure for T1D. However, therapeutic options for T1D are again at a turning point. Years of effort to develop immune interventions are ultimately starting to pay off, with hints of progress in both new onset and preventative settings. We discussed the recently completed and ongoing clinical trials that have studied the efficacy and safety of several immunotherapeutic strategies targeting various mechanisms of autoimmunity, which are considered significant in disease pathogenesis. While more targeted immunotherapies with potentially fewer adverse effects get closer to the translation into clinical practice, new challenges may need to be faced. A better understanding of disease endotypes may facilitate the stratification of individuals to different treatment options. While moving forward, success lies in selecting which interventions are best suitable for which stage of the disease. Therefore, the timing and benefit/risk profile of candidate approaches should be considered carefully. It is also essential to conduct more clinical trials at T1D diagnosis to compare interventions. With the increasing interest in combination approaches, immunotherapeutic strategies targeting different aspects of the immune system are likely to be essential contributors to the future therapeutic landscape, together with the practice of individualized patient-tailored approaches, a change towards early intervention, and an emphasis on outcome measures.

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Country of origin: India

ORCID number: Sayantan Ray 0000-0002-6274-465X; Rajan Palui 0000-0002-2429-3595.

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