Published in final edited form as:

Curr Opin Immunol. 2017 December ; 49: 44–50. doi:10.1016/j.coi.2017.09.004.

Have we pushed the needle for treatment of Type 1 diabetes?

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Abstract

Studies with immunologics have shown that the natural history of Type 1 diabetes can be modified. These studies have targeted key mediators of the disease and recent analyses, together with studies in preclinical models have identified mechanisms that may be involved in the clinical effects. Several issues remain including specificity of the interventions, adverse effects of the treatments, and duration of their effects. Future studies are likely to include more specific approaches with agents such as cell therapies with selected immune regulatory subsets, antigen specific therapies, and combinations of agents with complementary mechanisms of activity.

Type 1 diabetes (T1D) is an autoimmune disease mediated by the destruction of β cells in the pancreas. Preclinical and limited clinical studies have incriminated CD8⁺ effector T cells as the mediators of β cell killing but the ways in which this final common pathway is activated are complex and involve autoreactive CD4⁺ and CD8⁺ T cells, B cells, and potentially other cells, failure of regulatory T cells (Tregs), as well as features of β cells that may affect their susceptibility to killing and apoptosis and also suggest potential therapeutic strategies (Figure 1).

Insights into the natural history of T1D

Recent studies of metabolic function and biomarkers indicate that the disease course is accelerated when more than one biochemically defined autoantibody is present (i.e. autoantibodies to GAD65, ZnT8, IA-2/ICA512, insulin, or islet cell antibodies (ICA)) [1–3]. Those with 2 or more autoantibodies and dysglycemia during an oral glucose tolerance test (OGTT) show high levels of β cell death (identified by measuring β cell derived *INS* DNA in the circulation) and have a 50–75% risk of disease diagnosis within 5 years [4]. These data have suggested that rather than a slow steady progression, there is a crescendo of β destruction within the 1½–2 years before diagnosis. From these observations, therapies may need to be specifically targeted to mechanisms based on timing.

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This review comes from a themed issue on **Autoimmunity**

Edited by Michael Lenardo and Bernice Lo

For a complete overview see the [Issue](#) and the [Editorial](#)

Conflicts of interest

Dr. Herold has a patent application for an assay to measure β cell death.

In addition, the rates of progression differ in children and adults and the responses to therapies in younger and older subjects may differ. In adults, the loss of β cell function is slower and retention of insulin secretion is more common [5]. Recent studies have highlighted immunologic differences as well. Autoantibody specificities may vary by age with young children most often showing reactivity to insulin. Despite the more aggressive disease progression in children, responses to teplizumab (anti-CD3 monoclonal antibody (mAb)), rituximab (anti-CD20), abatacept (CTLA4Ig), are more robust in the younger population (e. g. <15 years) compared to older subjects [6,7]. The reasons for this age effect are not known but similar differences in younger and older patients have been observed in other autoimmune diseases (e.g. systemic lupus erythematosus (SLE)) [8].

Immune modulators can change the disease course

Three decades ago, studies with calcineurin inhibitors showed that targeting T cell mechanisms would attenuate disease progression in new onset patients [9,10]. However, the adverse effects of cyclosporine A, concerns about chronic immune suppression, and the lack of long term efficacy led to the search for agents with more specific activity, less toxicity, and without the need for chronic administration. Table 1 summarizes results of these newer clinical studies. Some features of these trials are noteworthy.

Teplizumab and oteplizumab, two FcR non-binding anti-CD3 mAbs, have shown beneficial effects in patients with new onset disease who received a single or two courses of the drug. C-peptide responses, insulin use, and HbA1c levels were improved [11–16]. C-peptide is a surrogate measure of β cell mass: the ultimate goal of therapies is to preserve β cell mass, which would result in reduced dependency on exogenous insulin and improved glycemic control. Importantly, the drugs are not given chronically so the risks of immune suppression are minimized. Treatment beyond the new onset period was less effective than in those enrolled within 100 days of diagnosis, even with significant levels of stimulated C-peptide. It is possible that this reflects “maturation” of the immune response or even changes in β cells that make them unrecoverable. In addition to improvement in C-peptide, a *post hoc* analysis showed that teplizumab improved the frequency of individuals with a HbA1c < 7% (the recommended treatment target by the American Diabetes Association ADA [17]) and used less than 0.25 U/kg/d of insulin (a dose that had been used for prevention in non-diabetic relatives in the DPT-1 trial) [11].

Recent studies with samples from two clinical trials of teplizumab have suggested that the partial agonist induces a phenotype of “exhaustion” or “partial exhaustion” in CD8+ T cells in clinical responders. In responders, CD8+ central memory T cells are expanded but these cells express low levels of IL-7 receptor (IL-7R) and in a transcriptome analysis, CD8+ cells expressing EOMES, TIGIT, and KLRG1 were increased [18,19**]. When the cells were challenged with a soluble ligand for TIGIT and anti-CD3 + CD28 mAbs, activation genes were downregulated indicating that TIGIT signaling may deliver an inhibitory signal with the potential to provide tolerance. Consistent with this concept of inducing non-responsiveness in the CD8 compartment, reduced expression of genes associated with the IL-7R pathway and T cell receptor signaling in memory T cells were also associated with improved prognoses in other autoimmune diseases, such as SLE and anti-neutrophil

cytoplasmic antibody (ANCA) associated vasculitis, whereas normal T cell receptor signaling in memory T cells was associated with a poor prognosis [20*,21].

Alefacept (LFA3Ig) binds to CD2, expressed by CD4+ and CD8+ effector memory T cells. A 12-week course of treatment was shown to improve C-peptide responses 18 and 24 months after diagnosis compared, to placebo-treated subjects. As in patients with psoriasis who were treated with alefacept, the drug caused a decrease in circulating effector memory T cells and the Treg:Teff ratio was increased [22,23]. It is notable that there was a decrease in the rates of total and severe hypoglycemia — the most frequent complication of T1D and a clear beneficial clinical outcome since insulin induced hypoglycemia represents the major impediment to tight glucose control. Retention of endogenous β cell function has been associated with reduced risk of hypoglycemia, a clinical benefit of immune therapy.

Eliminating B cells with anti-CD20 mAb (Rituximab) improved C-peptide responses, reduced insulin requirements, and reduced HbA1c levels after 1 year but the effects of the drug treatment did not persist at 2 years [24,25]. The mechanistic studies from this trial illustrate a number of barriers of transient B cell depletion to achieving lasting tolerance. Pathologic T cell responses were unaffected [26]. Importantly, the impairments in peripheral and central B cell tolerance checkpoints, that are found in patients with T1D, RA, and other autoimmune diseases, returned in the repopulated B cells after depletion with anti-CD20 mAb [27]. This experience highlights the needs for drug combinations targeting multiple cell types together or even sequentially.

Other therapies are in trials. The combination of antithymocyte globulin (ATG) and granulocyte colony-stimulating factor (G-CSF) may have an unconventional mechanism than thymoglobulin alone since the latter did not improve C-peptide responses after 1 year whereas a pilot trial of the combination suggested improved C-peptide [28,29]. The effects of G-CSF have been postulated to involve enhancement of Tregs or even β cell recovery.

Repairing dysregulation: Tregs, IL-2

Increasing the number and function of Tregs has been under intense study because of their central role in regulating autoimmune responses. Dysfunctional Tregs, that produce IFN γ and have impaired responses (i.e. pSTAT5) to IL-2 have been identified in patients [30]. A disease susceptibility allele, thought to impair Treg function, resides in the IL-2 receptor α chain (IL-2R α) locus. More recently, increased expression of IL-6 receptor (IL-6R) and responses to this inflammatory cytokine have been shown in Tregs before diagnosis [31].

Clinical trials have addressed whether exogenous IL-2 can enhance Treg numbers and function as has been accomplished in other settings [32,33]. In a trial combining rapamycin with a relatively high dose of IL-2, C-peptide responses transiently deteriorated which has been attributed to the effects of the high dose IL-2 on expanding natural killer (NK) and effector T cells and eosinophils [34]. Subsequent studies by two groups have aimed to identify doses of the cytokine that would selectively expand Tregs without increasing pathologic cells. To address the short half-life of the drug and erratic drug levels,

modifications to prolong the half-life of the cytokine are being tested ([ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT02411253) Identifiers: NCT02411253).

An alternative strategy is to administer Tregs. Initial studies used polyclonal Tregs. Children receiving autologous Treg infusions had increased C-peptide levels, and decreased insulin requirements, with 2 out of 12 participants being insulin independent one year later [35^{*}]. In a trial of adults with recent onset of T1D, autologous Tregs, that were expanded *ex vivo* were well tolerated in a Phase I study. Interestingly, the impaired pSTAT5 signaling that was found in the freshly isolated cells was remedied during the expansion process. These results have prompted a second trial with polyclonal Tregs to augment survival (the first phase half-life of cells in the circulation was 19.6 days, but it was ½ year in the second phase) and expansion with low-dose IL-2 ([ClinicalTrials.org](https://clinicaltrials.gov/ct2/show/study/NCT02772679) identifier: NCT02772679) [36^{*}].

Antigen therapies

Immunizations with two antigens — insulin and glutamic acid decarboxylase 65 (GAD65) have been tested with different routes and adjuvants (Table 1). The Diabetes Prevention Trial in 2005 found that oral insulin in at-risk relatives did not delay or prevent T1D, but a subgroup with higher insulin autoantibody (IAA) levels had a lower annualized diabetes rate with oral insulin (7.5 mg/day) [37]. A repeat oral insulin trial (TN07), the largest prevention trial to date, also failed to show clinical benefit, although there was significant improvement in a cohort with impaired first phase insulin responses. This unexpected result again highlights the need to tailor specific therapies to the appropriate subjects. (unpublished, presented at the American Diabetes Association Scientific Sessions 2017). Question about the dosing of insulin used in that study has been raised by data from the Pre-POINT study that found an immunologic effect at doses that are higher (67.5 mg/d) than those tested in the DPT-1 and TrialNet studies [38].

Although immunization with GAD65/alum failed to improve C-peptide responses in two trials [39,40], trials are ongoing with this antigen in combination with other compounds, including Vitamin D ([ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT02352974) Identifier: NCT02352974, NCT02387164), Vitamin D and Ibuprofen ([ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT01785108) Identifier: NCT01785108), Vitamin D and etanercept ([ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT02464033) Identifier: NCT02464033), and GABA ([ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT02002130) Identifier: NCT02002130).

Thus far, clinical trials have not been able to show that targeting a single autoantigen can induce a broad, sustained response in patients with or at risk of T1D. However, a recent publication has shown that immunization with a proinsulin peptide C19-A3 was safe, and C-peptide decline and increased insulin use were not seen over 12 months [41]. There clearly are gaps in our knowledge including the adjuvants, mode of delivery, doses, and even the choice of antigen(s) [42]. In addition, a new paradigm has been proposed whereby modifications of the antigens in β cells can create neoantigens for which central tolerance has not occurred [43–45].

β Cell factors

The role that β cells play in the decline in C-peptide after initial responses to immune therapies are not known. Intrinsic factors in β cells or their responses to stressors may contribute. Cell death pathways may be activated even after the factors that initiated them are no longer present (Figure 1). During endoplasmic reticulum (ER) stress, hyperactivity of the unfolded protein response, caused by ABL family of tyrosine kinases scaffolding the ER transmembrane kinase/endoribonuclease (RNase) IRE1 α , may promote apoptosis. The tyrosine kinase inhibitor imatinib is an antagonist to the ABL-IRE1 α interaction and can decrease β cell apoptosis and diabetes in NOD mice [46^{*}]. Preliminary data from a clinical trial support the activity of this pathway in patients (unpublished, presented at American Diabetes Association Scientific Sessions 2017). Talchai et al. described a mechanism of dedifferentiation leading to loss of β cells in Type 2 diabetes and experimental evidence has suggested that a similar loss of β cells may occur in T1D with development of a subpopulation that can resist immune killing [47,48^{*}]. This mechanism and the clinical finding of persistent C-peptide responses even after 50 years of T1D raise the possibility that β cell function may be recoverable — a hypothesis that needs further testing [49].

Conclusion

Recent studies have identified successful strategies for modulating Type 1 diabetes that need further exploration. Immune therapies can modulate the disease course and result in increased C-peptide responses with clinical benefit including improved glycemic control, reduced insulin requirements, and reduced rates of hypoglycemia. An extreme example of the effects of immune therapies are results from nonmyeloablative hematopoietic stem cell transplantation in newly diagnosed Type 1 diabetics in which 20 of 23 patients became insulin free for a mean of 31 months [50]. An immunologic strategy, occurring with anti-CD3 mAb and reflected by transcriptome studies of good prognosis in patients with autoimmune diseases is to induce features of exhaustion in the CD8 subset. The long-term failures of immune therapies may reflect the use of single agents when multiple immune cell subsets and pathways are involved and there are changes in the immune response over time. In addition, more information is needed about the role of intrinsic β cell factors in contributing to their demise. Combinations of the agents reviewed here as well as others that may be β cell protective or even restorative may lead to therapies that can finally deliver on the promise of disease reversal and immune tolerance.

Acknowledgments

Supported by grants R01 DK057846-11A1, 1DP3 DK101122-01, UC4DK104205 from the NIH, grant 17-2012-546 from the Juvenile Diabetes Research Foundation (JDRF), and a gift from the Howalt family.

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Identifying drugs that can induce similar changes in β cells could present novel therapies for T1D.

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Figure 1.

Type 1 diabetes pathogenesis and β cell protective factors. CD8+ effector T cells are considered the mediators of β cell killing, with the final common pathway involving a multitude of cells including autoreactive CD4+, CD8+, and B cells, failures of Tregs, and β cells that have changed susceptibility to killing and apoptosis. The pathogenesis is thought to begin with the release of β cell antigens, which antigen presenting cells (APCs) uptake and present to CD4+ and CD8+ T cells by Class II and Class I major histocompatibility molecules (MHC II and MHC I). This activates several pathways that ultimately lead to the immune destruction of β cells, via FasL-mediated apoptosis, release of chemokines and cytokines, and direct cytolytic killing. Recent studies have focused on new therapeutic targets that may help protect β cells from immune attack (highlighted in blue). These include therapies that target immune dysregulation, such as IL-2 and Treg infusions. There is also interest in understanding how intrinsic factors in β cells affect their response to immune attack and immune therapies. Endoplasmic reticulum stress may contribute to β cell death, and the tyrosine kinase inhibitor imatinib may inhibit this pathway. There is also some evidence that β cell dedifferentiation contributes to the pathology of T1D, with a subpopulation that is able to resist immune killing, which has increased expression of immune inhibitory proteins like PD-L1. Therapies that target these protective factors, used in combination with other immune therapies, could be beneficial for the treatment of T1D.

Table 1

Recent clinical trials for treatment and prevention of T1D

Therapy category	Agents	Results
Antigens	Insulin/proinsulin	Human trials of oral, nasal, and subcutaneous insulin have not had dramatic success [37,51–54]. Antigen, dose and method of delivery appear to be important [38,42]. In a repeat of the DPT-1 oral insulin trial, in relatives with at least 2 autoantibodies and impaired insulin response oral insulin delayed T1D onset by an average of 31 months (presented at the American Diabetes Association Scientific Sessions 2017). A recent study of the proinsulin peptide C19-A3 has shown that immunization with the peptide was safe, and C-peptide decline and increased insulin use were not seen over 12 months [41].
	GAD65/Alum	Initial trial suggested that GAD-alum could help preserve residual insulin secretion, but later studies could not replicate these results [39,40,55]. In the DiAPREV-IT 1 clinical pilot trial, GAD-alum was given to children at risk of developing T1D. Initial results from this study show that GAD-alum treatment did not have a significant impact on T1D onset (unpublished, presented at American Diabetes Association Scientific Sessions 2017). There are multiple active clinical trials using GAD65 in combination with other compounds, including Vitamin D (ClinicalTrials.gov Identifier: NCT02352974 , NCT02387164), Vitamin D and Ibuprofen (ClinicalTrials.gov Identifier: NCT01785108), Vitamin D and etanercept (ClinicalTrials.gov Identifier: NCT02464033), and GABA (ClinicalTrials.gov Identifier: NCT02002130).
T cell agents	Anti-CD3 mAb (teplizumab, otelixizumab)	Efficacy demonstrated in 6 randomized clinical trials [11,14–16,56,57] did not improve disease course at lower doses [58]. Some sub-groups seem more likely to respond than others, such as those with lower HbA1c or insulin use, or those with fewer Th1-like cells [56]. Ongoing clinical trial for at risk relatives (ClinicalTrials.gov Identifier: NCT01030861) and new-onset patients (ClinicalTrials.gov Identifier: NCT02000817).
	Alefacept	15 months after their last dose, the treatment group had better β cell function, lower exogenous insulin requirements, and fewer major hypoglycemic events [23].
	ATG +/- GCSF	Modest improvement in C-peptide at 1 year [29]
B cell agents	Rituximab	A 4-week course delayed the decline in C-peptide levels over 1 year [25], but the effect was lost at the end of 2 years [24]
Costimulatory blockade	Abatacept (CTLA4Ig)	Improved C-peptide responses for 2 years with continuous treatment [59].
Anti-inflammatory agents	Canakinumab (anti-IL-1 mAb)	No preservation of C-peptide [60]
	Anakinra (IL-1RA)	No preservation of C-peptide [60]
	Etanercept (soluble TNF receptor)	In pilot study in pediatric patients, lower A1c and improved C-peptide were observed [61]
Regulatory T cell	IL-2 + Rapamycin	An increase in the number of regulatory T cells was observed but there was also impaired β cell function [34]
	IL-2	Ongoing clinical trial to assess the clinical efficacy of IL-2 for T1D (ClinicalTrials.gov Identifiers: NCT02411253)
	Tregs +/- IL-2	In another clinical trial, one year after study inclusion, 8/12 participants treated with Tregs still required <0.5 UI/kg body wt of insulin daily vs. 2/10 of the untreated group. 2 participants receiving Tregs were able to stop exogenous insulin. However, the benefit of Tregs seems to decrease with time [62]. Phase I was not powered to assess efficacy, but several individuals exhibited stable C-peptide levels out to 2+ years after transfer [63] (ClinicalTrials.gov Identifier: NCT01210664) (ClinicalTrials.gov Identifier: NCT02772679)
β cell agents	Sitagliptin with omeprazole	Did not improve C-peptide responses at 1 year [64]
	Imatinib (tyrosine kinase inhibitor)	At 1 year, the treatment group had more preservation of β cell function, and reduced exogenous insulin requirements, particularly in the first 6 months of treatment (unpublished, presented at American Diabetes Association Scientific Sessions 2017)