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2011 Update: Antigen Specific Therapy in Type 1 Diabetes

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Abstract

Purpose of Review—Update on the clinical trials using antigen specific therapies in autoimmune diabetes.

Recent Findings—Type 1 diabetes is now a predictable disease with the measurement of islet autoantibodies, and the incidence is increasing dramatically. Safe and effective interventions are needed to stop the underlying autoimmune destruction of insulin producing beta cells. Beta cell antigens, insulin and glutamic acid decarboxylase, are being used to preserve endogenous insulin production in individuals with new onset diabetes and to prevent diabetes. The results of antigen specific immune intervention trials are reviewed and consideration is given to future directions for inducing tolerance in type 1 diabetes.

Summary—Antigen specific immune therapies act by enhancing regulatory T cell function, in animal models often locally and selectively in islets or pancreatic lymph nodes, while inhibiting effector T cells. This therapeutic pathway provides a safe treatment to preserve beta cell function in new onset diabetic individuals with the GAD-Alum vaccine being the most extensively studied therapy. Insulin is being used in many forms to prevent diabetes and stop the underlying autoimmune process. For the future, combination immune therapies targeting different pathways in the immune system will be needed to effectively induce sustained tolerance in type 1 diabetes.

Keywords

diabetes; autoimmunity; islet antigens; therapies

Introduction

Type 1A diabetes (T1D), the immune mediated form of diabetes, is a chronic autoimmune disease in which there is specific immune destruction of the insulin producing pancreatic β-cells. T cells as well as other mononuclear cells cause insulitis ultimately resulting in β-cell death, decreased insulin production, and a lifelong requirement for insulin therapy (1).

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Despite treatment with insulin therapy long-term complications, including nephropathy, retinopathy, neuropathy, and cardiovascular disease, can result (2; 3). Over the last two decades, the incidence of T1D has doubled especially in children less than five years of age (4; 5). The Diabetes Control and Complications Trial (DCCT) found that 20% of patients studied, who were within 5 years of diagnosis, had remaining insulin production (0.2–0.5 pmol/ml) (6); at this time immunologic intervention can potentially save beta cell function and reduce reliance on insulin administration. Even partial beta cell function is beneficial as patients that maintain endogenous insulin production have better metabolic control than those who rely solely on exogenous insulin (7), and improved metabolic control reduces the long-term complications from diabetes (8). Therapies that halt beta cell destruction can result in continued endogenous insulin production, greatly improving metabolic control, reducing hypoglycemia, and decreasing the prevalence of complications in T1D. Therapies aimed at altering the underlying autoimmune process in T1D are actively being investigated with monoclonal antibodies to anti-CD3 (9–12) and anti-CD20 (13) showing preservation of beta cell function after a year. Treatment with a single course of an anti-CD3 monoclonal antibody can result in endogenous insulin production five years later (14). However these therapies are not without side effects and concerns regarding immune suppression. Antigen specific therapies offer an excellent safety profile while still having efficacy, because they can either selectively eliminate islet-reactive T cells, or, alternatively or in addition, induce islet-specific regulatory T cells that can act locally within pancreatic lymph nodes or islets without affecting general immune competence. This review focuses on the mechanism of action of antigen specific therapies and those agents currently being studied in T1D.

Mechanism of Action

Antigen specific therapy involves the administration of islet proteins peptides during various stages of the disease pathogenesis. The currently recognized antigens in human T1D include insulin, proinsulin, B-chain of insulin, glutamic acid decarboxylase, and zinc transporter 8 (ZnT8) proteins (15). Autoantibodies directed towards these peptides can be used to assess disease risk (16; 17). The amount, route of administration, timing of therapy in the disease process, and combination with an adjuvant all contribute to the effectiveness of a given antigen therapy. Most of our understanding regarding the effects of antigen therapy on the immune system comes from studies in the non obese diabetic (NOD) mouse, a spontaneous model of autoimmune diabetes as well as antigen-induced selective transgenic models (18; 19). From these studies we presume that T1D is a T cell mediated disease, at least in its effector phase, in which T cells that produce inflammatory cytokines such as IFN-γ and TNFα in conjunction with innate immunity and other inflammatory factors (such as IL-1β) cause beta cell death (1; 20; 21). Adaptive and natural regulatory T cells can both oppose the actions of autoreactive effector T cells in animal models. Antigen specific therapy can enhance adaptive regulatory T cell responses in humans as it appears that intradermal administration of proinsulin peptide can lead to a peptide specific IL-10 response (22) (regulatory cytokine) similar to inducing tolerance in allergy (23; 24). This IL-10 specific response is also observed when insulin B chain is administered intramuscularly in Incomplete Freund's Adjuvant (IFA) (25). IL-10 has anti-inflammatory properties, down regulating IFN-γ (26), and inducing T cells to become regulatory T cells in peripheral

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lymph nodes and lymphoid organs (27; 28). In addition, islet-antigen specific IL-10 responses were detected in healthy individuals while those who progressed to type 1 diabetes had both IFN-γ and IL-10 responses. Interestingly, the individuals with type 1 diabetes who had IL-10 responses developed disease later in life (>20 years of age), underlining the therapeutic potential of an IL-10 response to delay or prevent disease (29). In mice, for example after oral insulin administration, other cytokines such as IL-4 and TGF-beta can be induced (30; 31) – at present it is not fully known, which of these could also play a role after antigen-specific therapy in humans. The concept of preventing or treating a more T_H1 mediated disease such as type 1 diabetes by deviating the immune system locally to T_H2 still remains therefore rather attractive (32).

A potential major benefit of immunizing with antigens is the result of site-specific immunotherapy, because, at least in animal models, regulatory T cells only act where islet antigens are present, which limits their effect to pancreatic lymph nodes and the islets themselves (33; 34).

Insulin

There is a significant amount of evidence in the NOD mouse model and humans that insulin is a key target of beta-cell autoimmunity leading to T1D. A simple observation is that insulin is specific for beta cells and no other cells are destroyed in T1D, while other identified autoantigens such as GAD65, IA-2, and ZnT8 are not specific to beta cells (35). In the NOD mouse model, mutating a single amino acid in a specific insulin epitope (amino acids 9 to 23 in the B chain of insulin) recognized by T cells prevents all diabetes (36; 37). In humans the insulin gene is the second most important genetic determinant of T1D (polymorphisms of the MHC class II genes provide the most significant genetic risk). The protective genetic variant of insulin results in increased insulin expression in the thymus, likely resulting in deletion of autoreactive insulin T cells during T cell development (38–40). Animal studies have shown that decreased insulin expression in the thymus during T cell development leads to increased insulin specific T cells and T1D onset (41).

There have been multiple studies utilizing insulin, insulin peptides, and proinsulin peptides to stop islet autoimmunity and prevent diabetes outlined in table 1 (22; 42–45). Twenty years ago, the first diabetes prevention trial (DPT-1) used a low dose of daily oral insulin in order to prevent T1D. In this NIH sponsored study (TrialNet oral insulin) oral insulin was provided to first degree relatives of T1D patients with at least two islet autoantibodies in an attempt to prevent diabetes onset (17; 46). However, the administration of oral insulin did not delay progression to overt diabetes, but in post-hoc analysis individuals with high titer insulin autoanibodies benefited from treatment. In this group of patients, it was estimated that diabetes onset was delayed as much as five years (47). Since the analysis was a post-hoc subgroup analysis, a repeat oral insulin trial sponsored by TrialNet in individuals with multiple islet autoantibodies (including insulin autoantibodies) is currently underway (table 2) (42). One likely issue that negatively affected the success of the DPT-1 oral insulin trial is that, as compared to the mouse models, a very low insulin dose was used (1mg in mice versus 7.5 mg in humans per dose) and that the therapy was given daily, whereas less

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frequent dosing has shown to be more effective for some mucosal antigens in mouse models (48).

In addition to insulin, immunization with the insulin B chain in IFA has been used in T1D patients, showing induction of IL-10 producing regulatory T cells, but no effect on C-peptide preservation (25). Peakman and coworkers are studying peptides of proinsulin, recognized by autoreactive T cells, to induce regulatory responses and ultimately tolerance to insulin, however no clinical benefit has been noted as of yet (22). Alternative routes of insulin dosing include intranasal insulin administration, where two initial trials did not yield positive results (44), likely because the nasal insulin had been administered too frequently (48). Bayhill Therapeutics developed an intramuscular proinsulin DNA vaccine, which is currently in a phase 2 trial to stop islet autoimmunity in new onset T1D patients with some encouraging initial benefits on C-peptide preservation (ADA disclosure last year).

GAD-Alum

The most extensively studied antigen specific therapy to date is the GAD-Alum vaccine. The initial study was done in individuals with latent autoimmune diabetes of adulthood (LADA) showing preservation of c-peptide with a single dose. Dose finding studies followed, showing that only a specific dose of 20ug was effective. Notable is the fact the both lower and higher doses were not efficacious, again indicating the importance of dose in antigen specific therapy (49). The underlying mechanistic reasons for this dose dependency are unknown, which is a major obstacle in defining key biomarkers that could predict the efficacy of therapy on an individual basis. In a double blind, randomized placebo controlled trial, GAD-Alum injection delayed the loss of c-peptide production in new onset T1D children and adolescents following a single course of therapy. Follow up at 30 months showed a significant preservation of insulin secretion only in those individuals that received the GAD-Alum vaccine within 6 months of T1D diagnosis (50). Similar to the immune suppressive therapies anti-CD3 monoclonal antibodies and rituximab (anti-CD20 monoclonal antibody targeting B cells), one year after therapy loss of c-peptide secretion resumed at a rate analogous to the control groups. In these trials, there was evidence of an immunologic effect with the induction of GAD65 specific regulatory T cells and with B lymphocytes (increased GAD autoantibodies) (51). Recently, four year data has been reported with GAD-Alum treatment demonstrating significantly better preserved fasting c-peptide in GAD treated subjects. The safety profile after four years is excellent revealing no treatment related adverse events (52) and larger phase 2/3 trials are underway (table 2).

Future Directions

Antigen specific therapies have many beneficial effects with regards to safety profiles and specificity in the mechanism of action. At the present time, more antigen specific therapies need to be tested in a rationale way as the GAD-Alum vaccine and the post-hoc analyzed subgroup of the oral insulin trial are the only approaches showing efficacy so far. Since the dose and route of administration appear to be crucial parameters, smaller proof-of-concept trials might be important to sort out such factors more rapidly and, at the same time, define key biomarkers. One such biomarker might be the existence of autoantibodies to a given

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islet antigen: As proposed by Harrison (53) and recently validated in a wet-lab based on valid *in silico* predictions by Entelos (Bresson et al. unpublished), individuals who generate autoantibodies to an islet antigen might be more prone to also make regulatory (for example T_H2 like) responses to the same antigen. Thus, there is now technology available provided by Entelos to use *in silico*computer aided, methods to assess dose and immune response in animal models with the potential to expand this technology to human disease (54). It will then also be useful to identify new epitopes of insulin and the newly discovered zinc transporter 8 and used in individuals with those specific antibodies. Last, the use and selection of adjuvants is also important and those adjuvants that enhance protective immune responses need to be considered with antigen specific therapy (i.e. IFA, Alum etc).

To prevent and ultimately cure T1D, a combination therapy approach will most likely be needed. The understanding of the immunopathogenesis in type 1 diabetes has increased considerably over the last several years (1) but clinical immune intervention is in the initial stages. We are now at a point in the immunotherapy field reminiscent of oncology developing the first chemotherapeutic agents, which now provide excellent five year survival rates for numerous malignancies. At the current time, there are no FDA approved therapies to block the autoimmune process in type 1 diabetes. However, there are now several single agent therapies (anti-CD3 monoclonal antibodies, rituximab, and GAD-Alum) that can delay c-peptide loss in newly diagnosed individuals with type 1 diabetes but none that sustain long lasting tolerance. There are currently many more single agent therapies under investigation (55). However, it is unlikely that we will be able to administer systemically acting immune modulators repeatedly and for a long duration of time to consistently delete autoimmune memory as well as newly formed self-reactive effector cells, but we are now at the point of combining successful single agents into suitable combination therapies with islet antigens. Work in preclinical animal models has demonstrated synergy with such combined therapies. For example, anti-CD3 monoclonal antibodies paired with intranasal insulin were able to reverse diabetes better than either single agent alone in a murine model of type 1 diabetes (56). Recently the Immune Tolerance Network (ITN) and Juvenile Diabetes Research Foundation (JDRF) partnered to make recommendations for developing combination immunotherapies in type 1 diabetes. In all, over 40 possible combinations of therapies could be considered (57). Combined therapies provide the benefits of synergy with the potential to lower efficacious doses which will lessen the side effects from long-term immune suppression. We favor providing an antigen specific therapy under the umbrella of an immune suppressive therapy such as anti-CD3 or an anti-inflammatory agent (IL-1 monoclonal antibody or receptor antagonist) currently under investigation (58; 59).

Conclusions

The field of immune intervention in type 1 diabetes is at an exciting time with the potential to prevent and induce tolerance in diabetes. Antigen specific therapies act by inducing adaptive regulatory T cells that then act locally at the site of insulitis in the pancreas or the pancreatic lymph nodes. Clinically, the GAD-Alum vaccine has shown efficacy in delaying the loss of endogenous insulin production and oral insulin in an antibody positive subset of patients as well as a pro-insulin expressing DNA vaccine in a small number of individuals

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have provided encouraging data while all having an excellent safety profile. In the future, antigen-specific therapies have the potential to become alone-standing therapies when given early enough to prevent T1D in those at risk. In addition, combination therapies with systemically acting immune modulators (either anti-inflammatory or anti-T cell) targeting different pathways in the disease pathogenesis, raise the level of optimism over the next decade.

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Key points

- Antigen specific therapies selectively eliminate islet-reactive T cells and induce regulatory T cells that can act locally within pancreatic lymph nodes or islets without affecting general immune competence.
- Oral insulin may delay the onset of type 1 diabetes up to seven years in first degree relatives of type 1 diabetic individuals with high titer insulin autoantibodies.
- Immunization with GAD-Alum preserves insulin secretion (measured by c-peptide) after 30 months in individuals that received the vaccine within 6 months of type 1 diabetes diagnosis.
- In the future, antigen specific therapies have the potential to become stand alone therapies when given early enough to prevent type 1 diabetes in those at risk.

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Table 1

Completed antigen specific trials in type 1 diabetes

Stage of disease	Study Title	Agent	Comment
Prevention	TrialNet oral insulin	Oral insulin	Delay of overt diabetes onset in 1st degree relatives of T1D patients with high titer insulin autoantibodies
Prevention	Intranasal insulin	Nasal insulin	No effect on delay/prevention of type 1 diabetes when given daily; ongoing trials are using less frequent administration of intranasal insulin
New onset intervention	GAD vaccine	GAD-alum	Delay in loss of c-peptide in those with T1D < 6mo from baseline
New onset intervention	HSP60	DiaPep277	Heat shock protein administered in several trials with limited efficacy; likely blocking innate immune system inflammation
Recent onset intervention	Immunization with insulin B chain	Insulin B chain + IFA	Increased IL-10 producing T cells but no effect on c-peptide in a small pilot study
Intervention	Proinsulin peptide immuno-therapy	Intradermal proinsulin peptide	Increased IL-10 production from peptide-specific T cells after 3 months of treatment

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Table 2

Ongoing antigen therapy trials in type 1 diabetes

Study Title	Agent	Phase	Patient Population	Clinicaltrials.gov
*TrialNet Oral Insulin	Oral Insulin	3	≥2 islet autoantibodies (including insulin) for T1D prevention	NCT00419562
*Intranasal insulin for the prevention of T1D	Intranasal Insulin	2	Prevention for at risk individuals	NCT00223613 NCT00336674
TrialNet GAD	GAD-alum	2	New onset T1D	NCT00529399
Diamyd GAD	GAD-alum	3	New onset T1D	NCT00723411
Study of BHT-3021 in T1D subjects	Proinsulin DNA Vaccine	1/2	New onset T1D	NCT00453375
*DiaPep277 in New Onset Adults	DiaPep277	3	New onset T1D	NCT01103284

* indicates trials currently enrolling at the time of publication