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Teplizumab therapy for type 1 diabetes

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Abstract

Importance of the field—Type 1 diabetes mellitus (T1D) is a T cell mediated autoimmune disease with selective destruction of β-cells. Immunological interventions are directed at arresting the loss of β-cell function with the promise that this will make it easier for patients to control their glucose levels.

Areas covered in this review—This review provides a summary of the preclinical and clinical research published between 1992 and 2009 using teplizumab and other anti-CD3 antibodies to arrest the loss of β-cell function in new onset T1D. Data from animal and human studies on the probable mechanism of action of teplizumab are also reviewed.

What the readers will gain—A broad perspective on the use of teplizumab in inducing disease specific tolerance.

Take home message—In phase I/II randomized control trials, in patients with new onset T1D, teplizumab slows the rate of loss of β-cell function over two years of follow up. Treated patients had better glycemic control and lower insulin requirements. Adverse events so far are mild and of limited duration. Phase III clinical trials are underway to confirm these results and to determine if two courses of drug have greater efficacy in arresting in loss of β-cell function.

Keywords

teplizumab; type 1 diabetes; immunologic tolerance; regulatory T cells; anti-CD3 antibody

1. Introduction

Type 1 diabetes (T1D) is a T cell mediated autoimmune disease with selective destruction of β-cells by auto reactive CD4+ and CD8+ T lymphocytes. In the non-obese diabetic (NOD) mouse model of T1D the disease can be transferred by infusing splenic CD4+ and CD8+ T cells into syngeneic immunocompetent recipients such as NOD neonates or adult irradiated NOD mice or NOD SCID mice [1]. An analogous human experiment is the development of T1D in recipients of bone marrow from donors with T1D [2]. Other immune cells apart from CD4+ and CD8+ T cells may also play a role in development of T1D. T regulatory cells may be important in controlling disease progression; and abnormal function and/or frequency of Fox-P3 expressing CD4+CD25+ Treg cells and IL4 and IL10 secreting Th2 and Tr1 cells in NOD mice and type 1 patients has been reported [3;4]. There is also data evidence implicating dendritic cells [5], macrophages [6;7] and B lymphocytes [8]. In NOD mice lacking B lymphocytes, the incidence of diabetes drops from 80 percent to 30 percent, and the disease develops a little later [8]. B lymphocyte deficient humans however, can still develop T1D

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providing convincing evidence that principal effector mechanisms are mediated by T cells [9].

2. The natural history of T1D

The autoimmune attack directed against β-cells occurs several years (5 years or more) before the clinical presentation of diabetes [10]. In the Diabetes Prevention Trial 1 (DPT1), loss of first-phase insulin secretion and confirmed islet autoantibodies (and lacking the protective HLA allele DQB1*0602) was associated with greater than a 50% risk of progressing to diabetes within the next 5 years [11;12]. Even after the diagnosis of diabetes there is still significant β-cell function and this explains why after treatment of the acute presentation there is a period of clinical remission – the "honeymoon phase" [13]. The decline in β-cell loss is often depicted as a linear decline but this is probably not true. Not only is there β-cell destruction but also some β-cell regeneration and the net decline reflects the balance between the two events [14]. It is likely that there is waxing and waning of the immunological destruction and acute loss may be followed by relative stability before further decline. The clinical remission after initial presentation is most likely due to recovery of insulin secretory capacity of β-cells present at diagnosis rather than due to regeneration of new β-cells. Unfortunately the remission is usually temporary and β-cell function declines so that many patients require full replacement doses of insulin within a few months. Immunological interventions have been directed both before the development of diabetes and after diagnosis in order to prevent decline in residual β-cell function.

3. Immunotherapy

Immunotherapeutic interventions in T1D have involved both antigen specific and non antigenic specific therapy [15;16].

3.1 Antigen specific therapy

Antigen specific therapies are directed at controlling the autoimmune process by inducing antigen specific tolerance. The rationale behind these interventions is to generate antigen specific regulatory T cells that induce anergy/deletion of autoreactive effector T cells [17; 18]. One of the challenges in T1D is identifying the pathogenic epitopes at the initiation of disease. After the onset of the autoimmune injury, epitope spreading makes identifying specific target antigens difficult [19]. The antigens used as tolerogens for T1D have included insulin and glutamic acid decarboxylase (GAD) [11;20]. So far this approach has not been successful. The DPT1 study failed to show efficacy with parenteral or oral insulin [11] in subjects who were at high risk for developing diabetes. There was a suggestion that a subgroup of individuals with high titers of anti insulin antibodies might have benefited; and a study is in progress to explore this. Two aubcutaneous injections of alum formulated GAD did not prevent a decline in β-cell function in new onset patients with T1D [20]. There is also a current study using human proinsulin encoding DNA plasmid vaccine [21] in new onset T1D.

3.2 Non antigen specific immunotherapy

Broad spectrum immunosuppressive agents such as cyclosporine, azathioprine, prednisone and anti-thymocyte globulin that deplete or inactivate pathogenic T cells have been tried in new onset T1D to see if they would prolong the clinical remission [22–27]. They did indeed decrease insulin requirements but the effect was modest and these drugs have both short and long term toxicity.

Even though non-antigen specific therapy is not directed at a specific population of pathogenic T cells, this is not to say that it cannot induce disease specific tolerance. Treatment with antiCD3 antibodies may be an example of such an approach (*vide infra*). The concept is of applying

non-antigen specific therapy that targets *activated T cells* wherever they are in the body. Hopefully when you have new onset diabetes, activated T cells are present only in the pancreas and no where else in the body.

4. Anti-CD3 antibodies

In 1979, Kung and Goldstein developed a mouse hybridoma cell line producing a IgG2a monoclonal antibody (ORTHOCLONE, OKT3) against a T cell surface antigen that showed promise in preventing rejection after allograft transplantation [28–31]. This OKT3 antibody was later identified as being specific to the ε chain of the CD3 complex which is the major signal transducing element of the T cell receptor[32].

The use of OKT3 in clinical use, however, was limited by its side effect of a "flu-like" syndrome consisting of high fever, chills, headache, and gastrointestinal symptoms (vomiting and diarrhea) and in severe cases pulmonary edema within hours of treatment [33]. This syndrome is due to OKT3 cross-linking the TCR/CD3 complex on the T cell surface and causing the T cell to release cytokines including tumor necrosis factor alpha (TNFα), interferon-γ, interleukins IL-2, IL-3, IL-4, IL-6, IL-10 and granulocyte-macrophage colony-stimulating factor. [34–38]. Binding by Fc receptor bearing cells (such as monocytes) to the Fc portion of OKT3 enhances the T cell receptor/CD3 complex crosslinking and increases the severity of this cytokine release syndrome. F(ab')2 fragments that lack the Fc portion do not result in as much cytokine release [39–46]. This observation led to the development of FcR non-binding anti-CD3 antibodies. The T cell activation also varies with the isotype of the anti CD3 specific antibody - the IgG2a class appearing to have the strongest effect [47–49]. OKT3, being a mouse monoclonal antibody results in development of human anti-mouse antibody that causes rapid clearance of injected OKT3 and reduces its efficacy. The solution to this problem is to humanize the antibody [39;40;50].

5. Humanized FcR non-binding anti CD3 specific antibodies

Two specific humanized FcR non-binding anti-CD3 antibodies have been studied in patients with T1D. hOKT3 γ1(Ala-Ala), (teplizumab), is a humanized version of the mouse monoclonal OKT3 antibody – retaining the same binding region of OKT3 but with amino acids at positions 234 and 235 of the human IgG1 Fc changed to alanine resulting in decreased Fc binding [35; 44]. ChAglyCD3 or otelixizumab is a humanized version of a rat anti-CD3 monoclonal antibody lacking a crucial glycosylation site in the Fc portion resulting in decreased Fc binding [40]. These two antibodies appear to have decreased cytokine release potential because of the changes in the Fc regions but maintain their immunomodulatory effects.

6. Proposed mechanisms of immunomodulation by anti-CD3 antibodies

Studies in the diabetic NOD mice have provided insights in the mechanisms of action of anti-CD3 therapy in T1D: (i) there appears to be an induction of self tolerance because syngeneic islet grafts transplanted into anti-CD3 treated mice survive indefinitely; and continuous immunosuppression was not needed. Moreover, the tolerance is specific because mismatched skin allografts are normally rejected [41]; (ii) treated NOD mice are resistant to the transfer of diabetes by diabetogenic spleen cells suggesting a regulatory T cell function [51]; (iii) treatment is most effective when the mice just develop hyperglycemia and not in prediabetic younger animals suggesting that the drug works on effector cells that are at present at onset of disease. Despite these observations, the cellular mechanisms by which anti-CD3 antibodies turn off the autoimmune destruction are not well understood. After infusion of the anti CD3 antibody, there is clearance of the immunological infiltrate from the islets [41]. During this initial treatment phase there may apoptosis of activated T cells; antigenic immunomodulation of the T cell receptor complex; and altered trafficking. After treatment has been completed there is a return

of the islet infiltrate, but it appears to be non destructive and confined to the periphery of the islets [41]. This altered immunological effect may reflect a resetting of T cell dependent active tolerogenic mechanisms [52;53] and several regulatory T cells and downstream signals have been implicated in this process. An induction of Foxp3+ CD4+CD25+ regulatory T cells [54;55] has been observed in pancreatic and mesenteric lymph nodes of treated mice [56]. The regulation appears to be via a transforming growth factor beta (TGFβ) mechanism because co-administration of TGFβ neutralizing antibody prevents the tolerizing effect of anti-CD3 therapy [52]. In the human clinical trials, a reduction in the CD4:CD8 ratio has been noted and this change seems to correlate with maintenance of C-peptide responses. The change in the ratio is not due to depletion of CD4 cells but due to an increase in a regulatory population of Foxp 3+CD8+CD25+ T cells [57].

7. Human trials with teplizumab and otelixizumab

In the phase I/II clinical trials, teplizumab and otelixizumab have been given to new onset T1D to determine whether these drugs will turn off the autoimmune process and prevent decline of residual β-cell function [58–61].

In the first study [58], Herold and colleagues recruited 24 subjects with new onset T1D. Inclusion criteria included diagnosis of diabetes in the previous six weeks, ages 71/2 to 30 years of age and positive for one of the autoantibodies against β-cell antigens (anti-GAD, anti-islet cell, anti-ICA512, or anti-insulin antibodies). In this open label study, the 12 subjects randomized to test therapy were given daily infusions of teplizumab for 14 days. The control group underwent the same metabolic and immunologic studies as in the drug-treated group, but the patients did not receive anti-CD3 mAb and were not hospitalized. Outcomes included T-cell analysis, area under the curve (AUC) C-peptide response to mixed meal tolerance tests, and HbA1c (glycated hemoglobin A1c) levels. The treatment group had maintenance of AUC C-peptide responses for one year whereas the control group showed significant decline ($p=0.01$). In the treatment group, the AUC C-peptide was 111.5 ± 50.2 nmol/l at time 0 and 114.2 ± 90.6 nmol/l at 1 year. In the control group on the other hand, the AUC C-peptide was 133.2 ±50.7 nmol/l at time 0 and 66.7 ± 53 nmol/l at 1 year. In keeping with the maintained β-cell function, the treatment group had lower HbA1c levels and lower insulin requirements compared to the control group.

There was a transient reduction in the circulating lymphocytes with a nadir occurring five days after treatment with levels returning to normal two weeks after the last dose of the monoclonal antibody. The recovered lymphocytes are unlikely to be new T lymphocytes from the thymus because T receptor excision circles (TREC) - stable, nonreplicative DNA strands excised from T cells during TCR gene rearrangement in the thymus - were not present [62]. Clinical response was also associated with decreased CD4:CD8 ratio 30 days and 90 days after treatment. IL-6 and TNFα, were notably elevated after the second day treatment, but remained much lower than values typically associated with cytokine release syndrome. Other side effects included mild and moderate fever and anemia. A mild pruritic utricarial rash developed on the hand and occasionally the trunk and feet in about half of the treatment group. The rash appeared half way through the treatment course and resolved by day 30. Anti idiotypic antibodies developed in half of the treated group but were detectable in only one patient at one year.

A subsequent report evaluated this same cohort of patients but also included some additional subjects and reported their follow up data at 24 months – there were 24 subjects who got 12 to 14 day infusion of drug and 24 control subjects [37]. The analyses at 1 year of this larger cohort showed maintained AUC C-peptide in the treatment group (97.1 + 9.6 % of response at study entry) but significant decline in control group (53.1 + 7.6 % of response at study entry). In the second year however, there is gradual decline in AUC C-peptide responses in the treatment

group but the values are still significantly higher compared to the control group ($p<0.02$). Thus at 24 months the AUC C peptide was ~ 80 pmol/ml/240 minutes in the treatment group and ~35 pmol/ml/230 minutes in the control group. The treatment group also had lower HbA1c levels and lower insulin requirements compared to the control group in this second year. The main conclusion from this 2 year follow up data is that teplizumab is effective in arresting the β-cell decline the first year but that this effect is not sustained and that in the second year a decline in β-cell occurs. Dr. Herold and colleagues also recently reported maintenance of C-peptide levels in 4 drug treated subjects (different cohort) followed up to 5 years [60].

Taken together, these different cohorts of patients indicate that one 12 to 14 day course of teplizumab attenuates the decline of β-cell function for at least two years and possibly five years. These studies with teplizumab can further be correlated with clinical data using the other humanized anti-CD3 antibody, otelixizumab.

Otelixizumab was evaluated in a similar study - 80 new T1D patients were randomly assigned to receive 6 days of otelixizumab or placebo infusions [61]. β-cell function was assessed measuring C-peptide release following glucagons injection. Patients receiving otelixizumab had higher levels of C-peptide compared to the placebo group for up to 18 months. This effect of the drug was more pronounced in patients whose β-cell function at baseline was in the 50^{th} percentile or above. As with teplizumab treatment, treatment with otelixizumab did not completely arrest the decline in β-cell function and there was a gradual decline from 6 months to 18 months. The immune changes and adverse reactions were similar to those seen with teplizumab-transient lymphopenia, decreased CD4:CD8 ratio, headaches, gastrointestinal symptoms, arthralgias and myalgias, and rash. In addition, 30 of the patients in the treatment group reported a mononucleosis-like syndrome comprised of sore throat, fever, and cervical adenopathy [61]. In 21 of 22 patients with available samples, this syndrome was associated with a rise in EBV DNA that normalized between 6 and 12 weeks. This symptomatic reactivation of EBV was not reported with teplizumab therapy. Teplizumab patients, however, were younger and so fewer may have been EBV carriers. Also the cumulative dose of teplizumab used was lower than that used in the otlexizumab trial and this could have had an impact on EBV reactivation. The phase III studies with these two agents may provide additional information regarding the issue of EBV reactivation.

8. Potential use of teplizumab with other therapies

There is interest in combining teplizumab with other therapies. Teplizumab combined with standard therapy has been shown in a clinical trial to be effective in treating acute renal and renal-pancreas allograft rejection [63]. Hering and colleagues have also used teplizumab in combination with sirolimus and tacrolimus in islet transplantation with 4 of 6 subjects becoming insulin independent for 1 year [64;65]. It has also been proposed using teplizumab in combination with exenatide in new onset T1D. Teplizumab would turn off the autoimmune process and exenatide would reduce the rate of apoptosis resulting in an increase in β-cell mass and function [66].

9. Teplizumab in other autoimmune disorders

A phase I/II trial from 2002 examined the role of teplizumab in psoriatic arthritis [67]. In this trial, seven patients were treated with escalating doses over a period of 12–14 days. Six of the patients noted a decreased amount of inflamed joints and 63% noted reduction in joint pain.

10. Conclusion and Expert Opinion

A 12 to 14 day course of teplizumab therapy in new onset T1D results in stable β-cell function the first year after treatment and a gradual decline in the second year. C-peptide levels are

higher in the treatment group than in the control group at all time points. Current clinical trials are administering two courses of drug (at diagnosis and 6 months later) with the idea that the second course will prevent the decline that occurs in the second and subsequent years.

Adverse events reported so far seem to be mild and of limited duration. Fever, headaches, myalgia, nausea and vomiting, and pruritic rash are the commonest reactions. All the patients have lymphopenia which recovers at about 1 month. A case of thrombocytopenia was reported.

In the study using otelixizumab, EBV reactivation with infectious mononucleosis type symptoms was reported. This has not been reported in the teplizumab trials but that may reflect differences in patient population and cumulative dose. There also have not been any reports of lymphoproliferative disorder. It should be pointed out, however, that only small number of patients has received the drug and follow up limited to two years. Studies of longer duration on larger number of subjects are necessary to evaluate long term safety.

The treated patients have better glucose control and lower insulin requirements even though the drug does not completely arrest the decline in β-cell function. The Diabetes Control and Complications Trial (DCCT) showed that having some β-cell function is associated with lower risk of hypoglycemia; better glycemic control; and lower rate of microvascular complications [68]. Long term follow up of the DCCT cohort also showed what is referred to as the legacy effect [69] - that is tight control initially, translates into lower risk for microvascular complications even if control deteriorates at a later date. Thus decreasing the rate of decline in β-cell function may translate into improved glycemic control with less risk of hypoglycemia and lower incidence of long term complications.

It is now possible by HLA typing; measuring autoantibodies against β-cell antigens; and measuring first phase insulin secretion to identify individuals who are at 35 to 60 % 5 year risk for development of T1D [10;12]. If long term safety issues are resolved then it is likely that immune therapies like teplizumab will be used in at risk individuals to arrest the disease at an early stage and so prevent the development of diabetes.

It is the authors' opinions that the current clinical trials will confirm teplizumab's effectiveness in decreasing the rate of decline in β-cell function, and that the drug will be available for this indication within the next 5 years.

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Declaration of interest:

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Box 1

Drug summary.

Drug name	**Teplizumab**
Phase	**I/II**
Indication	**New onset Type 1 diabetes**
Pharmacology description/mechanism of action	**Not well understood but there appears to be a resetting of T-cell dependent active tolerogenic mechanisms**
Route of administration	**Intravenous**
Pivotal trial(s)	**Currently underway: The Protégé Studies; ClinicalTrials.gov identifiers: NCT00385697; NCT0090582; NCT00870818**