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Disease modifying therapies in type 1 diabetes: Where have we been, and where are we going?

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ABSTRACT

With more than four decades of clinical research and 25 years of clinical trials, much is known about the natural history of T1D before and after clinical diagnosis. We know that autoimmunity occurs early in life, that islet autoimmunity inevitably leads to clinically overt disease, and that some immune therapies can alter the disease course. In the future, we will likely conduct trials to more deeply explore mechanisms of disease and response to therapy, employ combinations of agents including those aimed at supporting beta cells, consider the use of chronic, intermittent therapy, focus studies on preventing progression from islet autoimmunity, and consider the potential benefits of studying children independently from adults. Much of this work will depend upon clinical trial networks such as Diabetes TrialNet. Such networks not only have the expertise to conduct studies but their sharing of data and samples also allows for discovery work by multiple investigators, laying the groundwork for the future. Working with patients, families, funders and industry, such collaborative networks can accelerate the translation of science to clinical practice to improve the lives of those living with T1D.

1. Introduction

Type 1 diabetes (TID) results from the immune-mediated destruction of the insulin-producing beta cells in the pancreas. This understanding is based on early descriptions of insulitis and beta cell destruction coupled with the identification of autoantibodies to islet antigens in individuals with TID [1,2]. In 1986, George Eisenbarth proposed his model of TID as a chronic autoimmune disease [3]. This model, which consolidated years of work from multiple investigators, emphasized the multi-step TID disease process, from genetic predisposition to immune activation to abnormal glucose tolerance to clinical TID. The model also highlighted the opportunities for therapeutic intervention, from primary prevention before autoimmunity has started, to secondary prevention after islet autoimmunity has begun, to tertiary prevention after clinical TID has presented but before complete beta cell loss has occurred. Dozens of high quality TID trials have been launched and completed over the past 30+ years, with both successes and failures. This article will provide some historical perspective and concepts for moving toward the next generation of TID trials.

2. Historical perspective: clinical trials and the natural history of T1D

2.1. First generation new-onset trials with clinical remission as endpoint

Following the general acceptance that TID is an autoimmune disease, trials began to test the hypothesis that immunotherapy could halt beta cell destruction. Results on more than 30 human trials were reported during the 1980s and 1990s [4]. These were primarily conducted in those already with clinical disease with the aim to achieve disease remission or prolong the "honeymoon phase" of TID. Remission was chosen as endpoint since it conceptually represented a clinical benefit. The archetype of these first generation trials in recent onset T1D evaluated the effects of chronic administration of cyclosporin (CSA) in newly diagnosed subjects. In a 1986 article, Feutren et al. reported a significantly higher complete remission rate 9 months after randomization in subjects with new onset TID treated with daily CSA (24.1%) as compared to untreated subjects (5.8%) [5]. Two years later, the Canadian-European Randomized Control Trial Group published similar remission rates [6]. Complete remission was defined as a fasting blood glucose < 140 mg/dL, post-prandial blood glucose < 200 mg/dL, and HbA1C < 7.5% without insulin treatment. While the CSA results generated optimism among researchers, clinicians, and patients, they also highlighted one of the potential

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pitfalls of chronic treatment; namely, toxicity. The Feutren group noted a 52% increase in baseline creatinine levels in the CSA treated group [5], and the Canadian-European group reported moderate interstitial fibrosis and/or moderate tubular atrophy in 7–8/40 subjects [6]. Hence, although CSA treatment appeared to induce clinical remissions in some subjects, the toxicity of CSA dampened enthusiasm for chronic immunotherapy as a clinical option for those with T1D.

2.2. Benefits of C-peptide preservation independent of remission

While these initial trials focused on remission as a clinically important endpoint, other work noted the benefit of preserved C-peptide secretion independent of clinical remission. The Diabetes Control and Complications Trial (DCCT) demonstrated that a higher C-peptide level was associated with a lower risk of end-organ complications. These benefits were highlighted initially in a 1998 paper, suggesting that a level of 0.2 nmol/L or more resulted in less hypoglycemia and retinopathy [7]. A more recent analysis of DCCT suggested that any endogenous secretion affords clinical benefit [8]. This concept is echoed by islet transplant studies which show that although more C-peptide is better, any amount can restore hypoglycemia awareness [9,10]. Further correlative evidence of the importance of preserved C-peptide comes from the Joslin 50-year Medalist study, which evaluated characteristics of individuals with disease duration of 50 years or more. The Medalist study found that 67.4% individuals living with TID for 50 years or more had a random C-peptide level at least 0.03 pmol/mL [11]. While cause and effect are not known, these data imply a survival benefit in those with persistent residual secretion.

DCCT established the relationship between glycemic control and complication rates, including hypoglycemia and microvascular disease [12]. This led to the general acceptance that glycemic control is the most important variable in determining clinical course of TID. Moreover, DCCT demonstrated that intensive therapy helps maintain endogenous insulin secretion [13]. The long term follow up study of DCCT participants, Epidemiology of Diabetes Interventions and Complications (EDIC), suggests that glycemic control is most important early in disease: 10 years after the conclusion of DCCT, glycemic control in the intensive therapy and usual care groups was similar, but those who were in the original intensive therapy group continued to have better clinical outcomes [14]. From this, we might conclude that short term preservation of C-peptide early after diagnosis (which contributes to early glycemic control) would have long term clinical benefits. Other data has shown that restoring insulin secretion (with islet transplant) is beneficial even later in disease and can reverse microvascular complications [15].

2.3. Next generation of new onset trials with preservation of C-peptide as endpoint

The relationship between preservation of C-peptide and better clinical course led to acceptance of preservation of C-peptide level as an endpoint in clinical trials by both the FDA and EMA (European Medicines Agency) [16]. Around the same time, encouraging work had emerged from animal studies suggesting self-tolerance could be re-established in the setting of autoimmunity [17–20]. These pre-clinical studies have been nicely summarized by others [21]. A full discussion of immune tolerance is outside the scope of this article; however, a practical definition for human trials is a scenario wherein short-term immune therapy is used to produce long term remission of autoimmunity.

With the preservation of C-peptide as endpoint, the concept of short term treatment (potentially toleragenic or not) was tested in the next generation of trials, again in those with recent onset T1D. Notable Phase 2 clinical trials with negative results include studies of Mycophenolate Mofetil with and without dacluzimab [22], GAD65-alum [23], canakinumab/anakinra (anti-IL1/anti-IL1R) [24], and anti-thymocyte globulin (ATG) [25]. In contrast, at least three single therapy agents have been shown to beneficially affect the course of beta cell function in randomized trials in recently diagnosed subjects: anti-CD3 therapy with teplizumab and otelixizumab, anti B-cell therapy with rituximab, and T-cell co-stimulation blockade with abatacept. Additionally, though the trial was not fully enrolled due to a shortage of drug, recently reported results using Alefacept (anti-CD2) are suggestive of a beneficial effect [26].

As initially demonstrated in a pilot study of 24 participants with recently diagnosed T1D, a single 14 day course of teplizumab, an anti-CD3 human monoclonal antibody, stabilized C-peptide levels at 1 year in 9/12 treated as compared to 2/12 in the observation only group [27]. Subsequent phase 2 randomized studies (DELAY, with 58 subjects, and AbATE, with 52 subjects) also demonstrated profound effects, with preserved C-peptide at one and two years post randomization [28,29]. Surprisingly, an international, multi-center, phase 3 trial with teplizumab (the Protégé trial) ($n = 516$) failed to meet its primary (low HbA1c with limited insulin use) or secondary (C-peptide) endpoints [30], although post hoc analyses were positive in subgroups of subjects [31]. Another non-depleting anti-CD3 monoclonal antibody, otelixizumab, has shown similar preservation of beta cell function in new onset TID. In 2005, Keymeulen et al. published results of a European study demonstrating preservation of residual C-peptide. In their study, 80 newly diagnosed individuals were randomized to receive daily infusions of otelixizumab or placebo for 6 days and were then followed for 18 months. Side effects included manageable cytokine release syndrome symptoms and transient, but not-clinically significant, reactivation of latent Epstein Barr virus [32]. These results led to pilot studies aimed at reducing adverse effects. Unfortunately, a subsequent multi-center phase 3 trial with a reduced dose of drug failed to demonstrate benefit [33]. In 2009, Pescovitz et al. reported results of a phase 2 trial using rituximab, an anti-CD20 monoclonal antibody in which 87 individuals with recently diagnosed T1D were randomized to receive 4 weekly infusions or placebo over a month. Rituximab treatment delayed the decline in C-peptide levels by 8.2 months, resulting in a statistically significant preservation of beta cell function at 1 year, an effect which persisted at 2 years [34,35]. Results of a phase 2, randomized, placebo-controlled trial of abatacept in 112 recently diagnosed subjects were reported in 2011. Subjects received abatacept or placebo infusions at days 1, 14 and 28 followed by monthly infusions for a total of 27 infusions. At 2 years, C-peptide AUC was 59% higher in the treated group, with a 9.6 month delay in decline of C-peptide, although after 6 months, the decline in the treated group was parallel to the decline in the placebo group [36].

2.4. Prevention trials

The new onset studies demonstrated that some single agent therapies could alter the course of the disease, even if the effect was transient. Ideally, however, we would like to prevent clinical disease. In autoimmune diabetes, primary prevention refers to the prevention of islet autoimmunity, whereas secondary prevention refers to the prevention of clinical TID in those with autoimmunity. Prevention trials began in the 1990s based on the robust information about the natural history of disease prior to clinical onset as illustrated by George Eisenbarth [3].

Notable secondary prevention trials with negative primary outcomes include the Diabetes Prevention Trial-Type 1 Diabetes (DPT-1), the Deutsche Nicotinamide Intervention Study (DENIS), the European Nicotinamide Diabetes Intervention Trial (ENDIT), and the Type 1 Diabetes Prediction and Prevention Project (DIPP.)