Prevention of Type 1 Diabetes

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Abstract

There is a genetic predisposition to type 1 diabetes (T1D), particularly conferred by alleles present within the major histocompatibility complex. In susceptible individuals, an environmental trigger initiates an immune response. The immune infiltration into pancreatic islets results in beta cell damage, impairment of beta cell function, and potential destruction of beta cells. Consequently, there have been a number of studies using immune intervention in an attempt to alter the natural history of the disease. These studies have been conducted both before clinical manifestations of T1D, in an attempt to prevent the evolution of the disease, and after the clinical onset of T1D, in an attempt to slow progressive loss of beta cell function. This chapter summarizes the most important clinical trials that have been conducted to date.

Keywords

Type 1 diabetes · Immunotherapy · Prevention

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Type 1 diabetes (T1D) results from immune-mediated beta cell dysfunction, in genetically susceptible individuals in whom an environmental trigger initiates the immune response. Consequently, there have been a number of studies that have sought to interrupt the immune response in attempts to either prevent the development of clinical T1D or slow the progressive loss of beta cell function that continues after the clinical onset of T1D. This chapter will summarize those studies.

During the evolution of T1D, one can identify individuals with genetic predisposition by screening at birth for high risk HLA haplotypes (Ziegler and Nepom 2010). This has been done in both cohorts of newborn babies who have a first degree relative (FDR) – either parent or sibling – with T1D and in the general population (GP). Once identified, the risk of progression to T1D is not different in those with (FDR) or without (GP) a family history (Ziegler et al. 2013). These individuals are then followed at routine intervals for the development of diabetes-related autoantibodies. Once there are two or more autoantibodies, over the next two decades 85–90% of such individuals will progress to clinical T1D (Ziegler et al. 2013). Studies of interventions that are initiated in those who have genetic risk but no autoantibodies are "primary prevention" studies. Those initiated after the appearance of autoantibodies are "secondary prevention" studies (Skyler 2013a).

Alternatively, rather than screening newborns and following them longitudinally over time, potential risk of T1D can be sought be cross-sectional screening for autoantibodies among relatives of patients with T1D (Orban et al. 2009). Studies of interventions in these individuals also are "secondary prevention" studies.

Autoantibody-positive individuals progress to clinical T1D over time. Prior to meeting traditional diagnostic criteria for T1D, they will have progressive impairment of beta cell function, often manifested by dysglycemia – either impaired fasting glucose, impaired glucose tolerance (at the two-hour time point of a glucose tolerance test), or indeterminate glucose tolerance (values above 11.1 mmol/L at 30, 60, or 90 min during a glucose tolerance test). Other evidence of beta cell dysfunction also can be seen (Sosenko et al. 2012; Ferrannini et al. 2010). Studies of interventions in these individuals also are considered "secondary prevention" studies. Indeed, in 2015, there was issued a scientific statement by the JDRF, the Endocrine Society, and the American Diabetes Association, on the staging of presymptomatic type 1 diabetes (Insel et al. 2015). In this, those with genetic predisposition only are considered to have "Pre-Stage 1" T1D; those with autoantibodies are considered to have "Stage 1" T1D; those with dysglycemia are considered to have "Stage 2" T1D; and those meeting traditional diagnostic criteria or having symptoms are considered to have "Stage 3" T1D. Thus, stages 1 and 2 together represent "presymptomatic T1D" and intervention studies in these stages are "secondary prevention" studies. In this scheme, trials in individuals with Stage 3 T1D may test disease modifying therapies to slow loss of beta cell function, are considered "tertiary prevention" studies, or are considered by some as "intervention" studies rather than "prevention" studies. Studies in Stage 3 T1D may be in "recent-onset" T1D – generally defined as being initiated within the first 3 months after diagnosis, or in "established" T1D – generally meant to be after 4 months or more from diagnosis provided there is evidence of beta cell function above a predefined threshold.

Primary Prevention Studies

Primary prevention studies have used generally safe interventions, such as dietary manipulation or some form of antigen-based therapy. The ones conducted to date have usually involved a cohort identified at birth, but also have involved studies in autoantibody-negative, genetically at-risk children. One strategy tested was the removal of cow milk from infant formula, based on an epidemiologic analysis that suggests that earlier exposure to cow milk may serve as an environmental trigger (Gerstein 1994). The ambitious Trial to Reduce Incidence of Diabetes in Genetically at Risk (TRIGR) study, a multinational, randomized prospective trial, involved 77 centers in 15 countries and registered over 5000 newborns and randomized 2159 newborns over a 4.7-year period (TRIGR Study Group et al. 2011). A Finnish TRIGR Pilot Study enrolled 230 babies randomized to either a conventional cow-milk-based formula or a casein hydrolysate formula, to be initiated whenever the mother ceased breast feeding (Knip et al. 2010). It reported that babies fed the experimental formula were nearly 50% less likely to develop autoantibodies. The full-scale TRIGR study, using the same strategy, did not find a difference in appearance of autoantibodies by the time the participants had reached age 7 (Knip et al. 2014). Moreover, the development of T1D by age 10, the primary outcome of TRIGR, also did not find a difference in T1D between the two cohorts (Writing Group for the TRIGR Study Group et al. 2018).

Another Finnish study using a similar strategy used a third group that included an insulin-free whey-based formula, the concept being that bovine insulin in infant formula may serve as a trigger for T1D (Vaarala et al. 2012). That study randomized 1104 babies to the 3 formulae and found that there was 60% reduction in appearance of autoantibodies with the insulin-free formula.

The BABYDIET study, involving 150 infants, tested whether a gluten-free diet could reduce the appearance of autoantibodies, but it did not (Hummel et al. 2011). A small pilot study, named NIP, randomized 98 infants to either have supplemental docosahexaenoic acid or placebo (Chase et al. 2015). It had hoped to demonstrate a difference in cytokine profile, but failed to do so.

The pilot PRE-POINT Study tested the safety of high dose oral insulin in a group of 25 autoantibody-negative, genetically at-risk children ages 2–7 (Bonifacio et al. 2015). There were no safety issues and some suggestion of an effect on some immunologic measures. This was followed by another pilot study, the Pre-POINT-Early Study, which tested a refined oral insulin dosing schedule among 44 autoantibody-negative, genetically at-risk children age 6–24 months (Pre-POINT Early Study). That study was completed in December 2017, but results have not yet been reported. Another pilot study, similar to PRE-POINT, the PINIT study, using nasal insulin, involves 38 autoantibody-negative, genetically at-risk children ages 1–7, is expected to be completed in 2018 (PINIT Study).

Further primary prevention studies are underway or being planned. To facilitate them, the Freder1k-Study is screening 168,000 infants, from birth to 4 months of age, to identify infants with increased T1D risk for enrollment into primary prevention trials (Freder1k-Study). The GPPAD-POInT primary prevention study is

enrolling 1040 genetically at-risk infants age 4–7 months, who will be treated with oral insulin or placebo up until age 3 years, and then followed until age 7.5 years, with the primary outcome – the development of persistent confirmed multiple beta-cell autoantibodies or the diagnosis of diabetes (Ziegler et al. 2016).

Secondary Prevention Studies

Most secondary prevention studies have used either some form of antigen – insulin or GAD – or the vitamin nicotinamide. These studies evaluate time from randomization to clinical diagnosis of T1D. Two nicotinamide studies, DENIS (Lampeter et al. 1998) and ENDIT (2004), both were negative. Two studies using injected insulin, the DPT-1 Parenteral Insulin Trial (2002) and the Belgian Parenteral Insulin Trial (Vandemeulebroucke et al. 2009), were both negative. Two studies using oral insulin, the DPT-1 Oral Insulin Trial (Skyler et al. 2005) and the TrialNet Oral Insulin Trial (Writing Committee for the Type 1 Diabetes TrialNet Oral Insulin Study Group et al. 2017), which was based on a post hoc identified subgroup in the DPT-1 trial, also were both negative. An ongoing oral insulin trial, Fr1da, in 220 children, ages 2–12 years, with two or more diabetes-related autoantibodies, is using a higher dose of oral insulin treatment for 1 year with immunologic endpoints after two additional years of follow-up, and then following immune-positive versus immune-negative children for progression to dysglycemia or diabetes (Raab et al. 2016).

The Diabetes Prediction and Prevention (DIPP) study in Finland studied nasal insulin, but this too was negative (Näntö-Salonen et al. 2008). Another nasal insulin study, INIT-II, is in progress in Australia and should report soon (Trial of Intranasal Insulin in Children and Young Adults at Risk of Type 1 Diabetes (INIT II)). The DIAPREV-IT study, in Sweden, used a GAD-based vaccine and also was negative (Elding Larsson et al. 2017). A follow-up study, DIAPREV-IT 2, also in Sweden, is using the combination of a GAD-based vaccine plus vitamin D3 (Prevention Trial).

Two TrialNet studies using immune interventions, one with the anti-CD3 monoclonal antibody teplizumab (Teplizumab for Prevention of Type 1 Diabetes in Relatives), the other with the co-stimulation blocker abatacept (CTLA-4 Ig), have both nearly completed enrollment with subjects continuing to be followed for development of T1D. TrialNet has two additional prevention studies soon to be initiated. One, Methyldopa for Reduction of DQ8 Antigen Presentation in At-Risk Subjects for Type 1 Diabetes, will enroll 36 subjects, age 8 years or older, who have HLA-DQ8 and insulin autoantibodies, in a cross-over design, that will determine whether methyldopa can reduce DQ8 antigen presentation (Methyldopa for Reduction of DQ8 Antigen Presentation in At-Risk Subjects for Type 1 Diabetes). The other study, Hydroxychloroquine in Individuals At-risk for Type 1 Diabetes Mellitus, will randomize 201 individuals, age 3 years or older, with two or more diabetes-related autoantibodies, with the primary endpoint being development of diabetes or abnormal glucose tolerance (Hydroxychloroquine in Individuals At-risk for Type 1 Diabetes Mellitus).

Tertiary Prevention Studies

These are the most common studies using immune intervention. There have generally been conducted in recent-onset Stage 3 T1D. Initially, many were small pilot studies (Skyler 1987; Skyler and Marks 1993). Beginning in the mid-1980s, most studies have been randomized controlled clinical trials with sample sizes large enough to draw valid conclusions. These have been comprehensively reviewed recently (Skyler 2015; Skyler et al. 2017.). Here will be discussed the most important of these studies.

The first large randomized controlled clinical trials were with cyclosporine and with azathioprine. There were two large cyclosporine trials of 1 year duration – The French Study (Feutren et al. 1986) and the Canadian-European Study (1988). In both studies, there were attempts to stop insulin therapy or reduce insulin dose, with "remissions" being the primary outcome measure. In both cases, more remissions were achieved with drug than placebo, but unfortunately the remissions were not sustained despite continuing use of cyclosporine. An additional French study (Bougneres et al. 1988) that was not controlled (because "two controlled studies already showed benefit) confirmed that transient remissions could be achieved but again were lost despite continuing cyclosporine use for up to 3 years (Bougneres et al. 1990). A smaller cyclosporine study carefully assessed beta cell function and found beneficial effects when evaluated by stimulation with a mixed meal tolerance test but not by challenging with intravenous glucose or glucagon (Skyler et al. 1992).

Three randomized studies were conducted with azathioprine. Two Australian studies, one in adults (Harrison et al. 1985) and one in children (Cook et al. 1989), failed to demonstrate benefit. A third study, in which there was a 10-week course of corticosteroids followed by 1 year of treatment with azathioprine, showed improved beta cell function at 1 year (Silverstein et al. 1988).

The most extensively studied approach has been with anti-CD3 monoclonal antibodies, targeting activation of T-lymphocytes. Two different anti-CD3 monoclonal antibodies have been studied in clinical trials – teplizumab and otelixizumab. The first study with teplizumab was a small study, but it demonstrated sustained improvement of beta cell function for 2 years despite only 14 days of treatment at enrollment (Herold et al. 2002, 2005). The first study with olelixizumab was larger (80 randomized subjects) and had a 6-day course if treatment following randomization, with the primary outcome measure at 18 months, in which there was improvement of beta cell function which was carefully assessed with the hyperglycemic clamp technique (Keymeulen et al. 2005). At 48 months follow-up, although clamps were not done, subjects previously treated with drug had much lower insulin doses than placebo subjects, despite equivalent levels of glucose control as measured by A1c (Keymeulen et al. 2010). Two further Phase 3 studies with otelixizumab failed to show an effect, but were complicated by the fact that the dose was lowered to only one-sixteenth of that used in the original study (Aronson et al. 2014; Ambery et al. 2014).

Several additional studies have been conducted with teplizumab. In the Abate Trial, there was again beneficial effect, but teplizumab treated subjects could be

divided retrospectively into two groups – "responders" and "nonresponders" to treatment (Herold et al. 2013a). Responders were those who maintained C-peptide better than the randomized, but untreated, comparison group at 24 months, and the constituted about half of the treated subjects. Another study, the Delay Trial, enrolled subjects beyond the recent-onset period, between 4 and 12 months after diagnosis (Herold et al. 2013b). Those enrolled between 4 and 8 months showed beneficial effect on beta cell function, whereas those enrolled 9 months or longer after diagnosis did not. Two large Phase 3 trials with teplizumab were conducted. Unfortunately, the arbitrary primary outcome at 1 year required the combination of A1c <6.5% and insulin dose less than 0.5 units/kg/day (Sherry et al. 2011). This was not achieved, although improved beta cell function measured by C-peptide was seen both after 1 year and after 2 years (Hagopian et al. 2013).

The failures of achieving the primary outcome measures in the Phase 3 trials of otelixizumab and teplizumab represent major setbacks to the field, as this therapeutic approach remains promising (Skyler 2013b).

Phase 3 trials have also been conducted with a glutamic acid decarboxylase (GAD)-based vaccine, in which GAD was administered subcutaneously along with an aluminum hydroxide adjuvant (GAD-Alum). These were based on a pilot study which appeared to show benefit in a small subgroup (Ludvigsson et al. 2008). However, the Phase 3 trials failed to show improvement in beta cell function (Ludvigsson et al. 2012; A Phase III Study to Investigate the Impact of Diamyd in Patients Newly Diagnosed With Type 1 Diabetes (USA) – DIAPREVENT), a failure also shown in a large Phase 2 trial (Wherrett et al. 2011).

Another intervention taken to Phase 3 trials was a peptide component of heat-shock protein, a peptide named DiaPep277. The initial pilot study looked promising (Raz et al. 2001). The initial reports of the Phase 3 trial claimed to have benefit, but were retracted for fraud (Raz et al. 2014; Pozzilli et al. 2014).

A number of other immune interventions have shown transient benefit, including rituximab (Pescovitz et al. 2009, 2014), abatacept (Orban et al. 2011, 2014), alefacept (Rigby et al. 2013, 2015), and the combination of thymoglobulin (ATG) and granulocyte colony stimulating factor (Haller et al. 2015, 2016). A small pilot study suggested benefit with etanercept (Mastrandrea et al. 2009). In contrast, several other approaches have failed to show benefit, including mycophenalte mofetil alone or in combination with daclizumab (Gottlieb et al. 2010), interleukin-1-beta blockade with either canakinumab or anakinra (Moran et al. 2013), thymoglobulin alone (Gitelman et al. 2013), and an altered peptide ligand of insulin B-chain (Walter et al. 2009). Another study in recent-onset T1D using nonimmune therapy aimed at improving beta cell function combined sitagliptin and lansoprazole, but without effect (Griffin et al. 2014).

Several small pilot studies have evaluated safety of alpha-1-antitrypsin (Gottlieb et al. 2014), plasmid-encoded proinsulin (Roep et al. 2013), proinsulin peptide (Thrower et al. 2009; Alhadj Ali et al. 2017), low-dose interleukin 2 (Hartemann et al. 2013), insulin B-chain (Orban et al. 2010), dendritic cells (Giannoukakis et al. 2011), and regulatory T-cells (Bluestone et al. 2015). All of these were safe, but there was inadequate data to determine efficacy.

A controversial approach has been the use of autologous hematopoietic stem cell therapy (AHSCT). A Brazilian group conducted an uncontrolled study in young people within 6 weeks of diagnosis and reported that many could cease insulin therapy and had improved beta cell function (Voltarelli et al. 2007; Couri et al. 2009; Voltarelli et al. 2009). Another report summarized additional subjects treated in Poland and China, with similar results, but some morbidity and mortality (D'Addio et al. 2014). These studies all used high dose immunosuppression as well, making it unclear whether any beneficial results were due to the immunosuppression or the stem cells. A subsequent report found that in the Brazilian study, in those with prolonged remission baseline islet-specific T-cell autoreactivity persisted after transplantation, but regulatory T cell counts increased (Malmegrim et al. 2017). Clearly, more work is needed in this arena, including the need for randomized controlled trials.

Overall, the effects of immune intervention in recent-onset Stage 3 T1D have been disappointing. Although some studies have demonstrated transient beneficial effects, none has resulted in long standing persistence in improvement in beta cell function. Success may require the use of an approach that uses combined immunomodulation, perhaps together with agents that improve beta cell health.

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