Published in final edited form as:

Pharmacol Res. 2015 August ; 98: 3–8. doi:10.1016/j.phrs.2015.02.002.

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

Sandra Lord, MD*

Diabetes Clinical Research Program, Benaroya Research Institute, Seattle, WA, USA; Carla J Greenbaum, MD, Diabetes Clinical Research Program, Benaroya Research Institute, Seattle, WA, USA

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; sharing of data and samples allow 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.

Keywords

type 1 diabetes; clinical trials; disease modifying therapy; Diabetes TrialNet

Type 1 diabetes (T1D) results from the immune-mediated destruction of the insulin-producing beta cells in the pancreas. This understanding is based on early descriptions of insulinitis and beta cell destruction coupled with the identification of autoantibodies to islet antigens in individuals with T1D (1;2). In 1986, George Eisenbarth proposed his model of T1D as a chronic autoimmune disease (3). This model, which consolidated years of work from multiple investigators, emphasized the multi-step T1D disease process, from genetic predisposition to immune activation to abnormal glucose tolerance to clinical T1D. The

© 2015 Published by Elsevier Ltd.

*corresponding author at: Diabetes Clinical Research Program, Benaroya Research Institute, 1201 9th Ave, Seattle, WA 98101, USA, slord@benaroyaresearch.org.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

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 T1D has presented but before complete beta cell loss has occurred. Dozens of high quality T1D 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 towards the next generation of T1D trials.

1. Historical Perspective: Clinical Trials and the Natural History of T1D

First generation new-onset trials with clinical remission as endpoint

Following the general acceptance that T1D 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 T1D. 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 T1D 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 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.

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 T1D for 50 years or more had a random c-peptide level at least 0.03

pmol/mL (11). While cause and effect is 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 T1D. 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).

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 otelexizumab, 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, otelexizumab has shown similar preservation of beta cell function in new onset T1D. 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 otelexizumab 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).

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 T1D 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.) DPT-1 consisted of two trials using either parenteral (37) or oral insulin (38), both aimed at preventing or delaying onset of clinical disease in those with autoantibodies. Both DENIS and ENDIT trialed nicotinamide as a prevention therapy in individuals with islet autoimmunity (39;40). The DIPP study investigated whether administration of nasal insulin to individuals with genetic risk and autoantibodies could delay or prevent the development of T1D (41). Similar to the negative results from secondary prevention trials, the outcomes from primary prevention trials also proved disappointing. The Trial to Reduce IDDM in the Genetically at Risk (TRIGR) asked whether weaning to hydrolyzed casein formula instead of regular milk formula in genetically at risk infants could prevent or delay T1D (42). BABYDIET investigated whether delayed introduction of gluten in infancy could delay or prevent islet autoimmunity.

(43;44). Collectively, these prevention studies required screening of several hundred-thousand participants and the collective efforts of hundreds of investigators and clinical teams over many years. Although none of these trials met their primary endpoints, a post-hoc analysis of the DPT-1 oral insulin trial found up to a 10-year delay in disease onset in those with the highest levels of insulin autoantibodies (45). Most importantly, these studies confirmed pre-study risk estimates of development of clinical T1D in relatives, thus enhancing our understanding of disease risk and the natural history of T1D.

Islet autoimmunity progresses to T1D

It has been known for almost half a century that the risk of T1D is increased in family members as compared to those from the general population; overall ~0.3% of the general Caucasian population will develop T1D as compared with 5% of those with a relative with T1D, a 15 fold increase in relative risk. While non-HLA genes are also associated with disease, the risk of T1D is strongly linked to HLA class II DR3 (DRB1*0301-DQB1*0201) and DR4 (DRB1*0401-DQB1*0302) haplotypes, with the highest risk in those with DR3/DR4 genotype (46). Studies of relatives with genetic risk by family history and/or HLA type have quantified the risk for development of autoimmunity and T1D from birth. Antibodies usually appear early in life; 64% of babies destined to develop T1D before puberty will have antibodies by age 2 and 95% by age 5 (47). Whether evaluating prospective birth cohorts (48) or following relatives identified cross-sectionally (49–51), data on risk of progression from confirmed autoimmunity (2 or more antibodies) to onset of clinical disease is remarkably consistent. The 5 year risk of overt clinical disease in those with 2 or more antibodies is in the range of 40%, the 10 year risk is about 70%, and 15 years about 85%. The estimate therefore is that 11% per year will progress from autoimmunity to clinical disease, with the key point that essentially all of these individuals will eventually present with overt hyperglycemia and T1D.

The benefits of clinical trial networks: Diabetes TrialNet and Immune Tolerance Network

Much of the data on the natural history of disease prior to diagnosis referenced above has largely come from efforts of investigators collaborating in multicenter clinical trial networks due to the need to screen large numbers of subjects to identify those at risk and to follow them consistently over many years. Recent information about the natural history of disease after clinical diagnosis has also greatly benefited from the data available from multicenter clinical trial networks. For example, two NIH sponsored networks have been conducting T1D clinical trials for more than a decade. The Immune Tolerance Network (ITN) focuses solely on toleragenic strategies; its scope includes T1D as well as other autoimmune diseases, allergy, asthma, and transplantation. Type 1 Diabetes TrialNet is an NIH-sponsored international network of clinical centers with the aim of modifying the disease course pre and post clinical diagnosis. In both, network activities have provided a framework for collaborative decisions, establishing standard processes for scientific, ethical, and feasibility reviews of protocols, and consistency in trial design, clinical assays and study endpoints. This standardization provides added value to each individual trial by allowing data to be explored across studies; for example, quantification of the differences in fall of C-peptide post diagnosis according to age, as illustrated in Figure 1 (52). These networks have

also pioneered innovative ways to share clinical trial data with external investigators (ITN TrialShare).

Importantly, accompanying ancillary or mechanistic studies can be applied with consensus definitions of responders and non-responders to therapies using samples collected and handled in standard procedures. Moreover, as demonstrated by the nine trials in newly diagnosed patients conducted by TrialNet, networks with established clinical centers offer marked efficiencies and high quality in the conduct of multicenter trials (22;23;25;28;34;36;53). These studies recruited rapidly and were completed with a high degree of compliance allowing for confidence in the conclusions.

2. Future considerations

With solid data about the natural history of disease, and evidence that immune therapy can be administered safely and can somewhat alter the clinical course, what are the next steps for the field to consider?

What about the beta cell?

One issue is how clinical trials can address the beta cell side of the equation; these discussions have reinvigorated an older question: is beta cell death homicide or suicide? In other words, while there is clear and incontrovertible evidence that the immune system is a driver of T1D, does the beta cell contribute to its own dysfunction or death? Newer technologies have increased our understanding of beta cell stressors, and various measures of beta cell death, function, and visualization continue to be explored as clinical trial outcome markers. Moreover, pathology specimens and measures of insulin secretion long from diagnosis highlight that either not all beta cells are killed or that there is some form of regeneration or awakening of dysfunctional cells that can occur (54;55). Reducing the “stress” on the beta cell is not a new idea. While the DCCT and a small randomized trial in the late 1980s (56) suggested preservation of beta cell function in those receiving intensive insulin therapy, a recent randomized trial found no difference between early aggressive therapy and standard of care (53), suggesting that beta cell rest by insulin therapy post diagnosis has only a limited, and likely not very clinically relevant effect since intensive insulin therapy is standard of care. Similarly, the DPT-1 parenteral insulin trial at least partly “rested” the beta cell with yearly IV and daily low dose insulin therapy. While the primary outcome was negative, there was a suggestion that the IV insulin therapy may have reduced the immune response (57). Another approach to reducing beta cell stress is to support the beta cell during the disease process with glucagon like peptide-1 (GLP-1) agonists. There is limited human data, primarily in type 2 diabetes, on the effects of GLP-1 agents on beta cell secretion (58–60). Yet, it is likely that the next generation of T1D trials aiming to alter the natural history of disease will include beta cell directed agents.

Combination therapy

These therapies likely will be trialed in combination with other agents. Combination therapies, whether both “beta cell support” and a single immunomodulating agent or combinations of immune therapies with differing mechanisms, are expected in future T1D

Author Manuscript

Author Manuscript

Author Manuscript

Author Manuscript

trials. Such combination therapy might result in a more robust and prolonged benefit and offer the potential for reducing the risks associated with escalating or prolonged doses of single drugs. Combination therapy has been successful in other autoimmune diseases, and is commonplace in transplantation. Previous notable trials of combination therapy in new onset T1D include: IL-2 and rapamycin, which was halted early due to a transient decrease in C-peptide level in treated individuals despite an increase in Tregs (61); and mycophenolate mofetil with and without dacluzimab (22), which did not meet its primary endpoint, the preservation of C-peptide. The most aggressive approach towards combination therapy in newly diagnosed T1D is the autologous nonmyeloablative hematopoietic stem cell transplant (AHSCT). While the pooled data from AHSCT trials suggests it has a higher remission rate (59% at 6 months and 32% at 48 months) than with other approaches, there are significant risks, including neutropenic fever, serious infection, and even death (62). Other approaches have sought to reap some of the benefits of AHSCT with fewer adverse effects. A recent pilot study combining ATG and GCSF is suggestive of a beneficial effect on C-peptide in recently diagnosed subjects (63) despite the fact that previous trials with these agents separately were unsuccessful (25;64). The standard approach to combination therapies involves trialing each individually, either in separate arms or separate studies. This approach not only consumes valuable time and money, it also exposes potential participants to agents for which we have limited expectations. Moreover, if conducted sequentially, results may lead to discarding therapies that would be effective only in combination. On the other hand, if therapies are trialed in combination before being trialed separately, then the benefit of one therapy could be canceled out by the negative effect of the other therapy. Additionally, there could be risks and side effects seen with combination therapy that are difficult to sort out unless therapies are trialed separately. In recognition of these challenges, the regulatory and administrative hurdles involved in combination therapy trials are significant. Nonetheless, the next generation of trials will almost certainly involve combination therapies.

Chronic intermittent immune therapy for T

ID The next generation of trials may also reflect an increasing willingness to accept the risks of chronic, intermittent immune therapy rather than expecting a short course of therapy to have a long term beneficial effect. This paradigm shift relates to the extensive clinical experience with newer generations of immune therapies in individuals with other autoimmune disease. Immune tolerance, while somewhat feasible in allergy and transplantation, has not yet been achieved in autoimmune disease. Instead, individuals are treated chronically, and often intermittently with the aim to both provide symptomatic relief and reduce the long term consequences, such as joint destruction in rheumatoid arthritis (RA). Akin to the results seen in T1D trials, not all subjects with other autoimmune diseases respond to treatment. For example, in separate studies of RA therapy, rituximab and abatacept combined with methotrexate resulted in a clinically important benefit in only slightly more than 20% of subjects (65;66); yet both are approved for clinical use in RA. Individuals with other autoimmune diseases not only receive chronic therapy, they often switch drugs when one becomes inefficacious. New trials in individuals with T1D may begin to test such a paradigm; chronic, intermittent, and potentially sequential therapies.

Treating the disease: islet autoimmunity

Two very important changes in the approach to clinical trial design are also likely in the future. Currently, even though delaying or preventing onset of clinical diabetes in the “at-risk” population would be a clear and unambiguous benefit, conducting studies in the “at-risk” population is largely done only after evidence of efficacy is demonstrated in those with overt clinical disease. This is the process followed with two fully powered, ongoing prevention trials; TrialNet’s Abatacept Prevention Trial in relatives with two or more antibodies and normal glucose tolerance which followed the positive results in the TrialNet new-onset trial (36) and TrialNet’s Teplizumab Prevention Trial in antibody positive relatives with abnormal glucose tolerance, following the successful AbATE and other anti-CD3 studies in recent onset T1D described previously. While the 5 year risk for developing overt clinical disease is maybe only 30–40% or 80% for each of these populations respectively, we now understand that *all of these individuals will eventually develop clinical disease*. Thus, one could consider that islet autoimmunity (defined as having 2 or more autoantibodies) *is* a disease in the same way that we consider hypertension a disease. We treat hypertension to prevent its long term complications (e.g. stroke, coronary artery disease). Among people with hypertension, the 5 year risk of a coronary event or stroke is about 2–3/100 (67). As noted above, among people with 2 or more diabetes antibodies, the 5 year risk of T1D is much greater: 35–40/100. Moreover, treating 100 people for hypertension prevents 2 strokes or coronary events, whereas TrialNet’s ongoing prevention trials are aiming for a significantly greater benefit in preventing T1D. Thus, there are two reasons that one may expect to see future trials in those with islet autoimmunity without prior demonstration of therapeutic efficacy in those with overt clinical disease; (a) prevention or delay of overt clinical disease is a clear benefit, (b) islet autoimmunity is a disease with inevitable consequences. Moreover, the attendant metabolic dysregulation post clinical diagnosis may impair the efficacy of immune or beta cell supporting therapies to alter disease course.

Study children independently from adults

A second change in future clinical trial design involves how we consider conducting clinical trials in children. In general, clinical trials have tested therapies first in adults before enrolling children. However, we now understand that adults and children with autoimmune diabetes have different clinical courses. This means that children with antibodies progress to clinical disease at a faster rate than adults, younger children start with less C-peptide at the time of diagnosis than teens and adults, and the rate of fall of insulin secretion post diagnosis is faster in children as compared with adults (68;69). C-peptide declines about 50% in the first year after diagnosis in individuals diagnosed as children, whereas the 1 year decline is 20% in adults (68). These observations lead to the expectation that these early differences may have long term consequences, a notion recently confirmed in a study of individuals with a long duration of diabetes: as compared with those diagnosed as children, many diagnosed as adults continue to have endogenous insulin secretion (54). As shown in Figure 2, T1D Exchange data shows that among individuals with duration of disease 20–40 years who were diagnosed after age eighteen, 19% have detectable c-peptide, whereas this value is 7% in those diagnosed before age eighteen.

Consequently, it is those diagnosed with T1D as children that are more likely to benefit from an intervention to preserve their beta cells. Moreover, differences in clinical course highlight that results of therapies trialed in adults may not reflect efficacy in children. For example, though the Phase 3 Teplizumab trial did not meet its primary endpoint; a post-hoc analysis suggested efficacy in children aged 8–11 years (30).

3. Summary

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; sharing of data and samples allow 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.

Acknowledgments

The authors thank the NIDDK, NIAID, JDRF, ADA, and Helmsley Trust for their funding of clinical trials and clinical research in T1D through ITN, Diabetes TrialNet and the T1D Exchange. We thank our colleagues at ITN, Diabetes TrialNet, and T1D Exchange for their helpful discussion over the years. Lastly, we thank the patients and families for their invaluable contributions to T1D research.

Reference List

1. Bottazzo GF, Florin-Christensen A, Doniach D. Islet-cell antibodies in diabetes mellitus with autoimmune polyendocrine deficiencies. *Lancet*. 1974; 2:1279–1283. [PubMed: 4139522]
2. Gepts W. Pathology and anatomy of the pancreas in juvenile diabetes mellitus. *Diabetes*. 1965; 14:619–633. [PubMed: 5318831]
3. Eisenbarth GS. Type I diabetes mellitus. A chronic autoimmune disease. *N Engl J Med*. 1986; 314:1360–1368. [PubMed: 3517648]
4. Staeva-Vieira T, Peakman M, von Herrath M. Translational mini-review series on type 1 diabetes: Immune-based therapeutic approaches for type 1 diabetes. *Clin Exp Immunol*. 2007; 148:17–31. [PubMed: 17349010]
5. Feutren G, Papoz L, Assan R, Vialettes B, Karsenty G, Vexiau P, Du RH, Rodier M, Sirmai J, Lallemand A. Cyclosporin increases the rate and length of remissions in insulin- dependent diabetes of recent onset. Results of a multicentre double- blind trial. *Lancet*. 1986; 2:119–124. [PubMed: 2873396]
6. Cyclosporin-induced remission of IDDM after early intervention. Association of 1 yr of cyclosporin treatment with enhanced insulin secretion. The Canadian-European Randomized Control Trial Group. *Diabetes*. 1988; 37:1574–1582. [PubMed: 2903105]
7. Steffes MW, Sibley S, Jackson M, Thomas W. Beta-cell function and the development of diabetes-related complications in the diabetes control and complications trial. *Diabetes Care*. 2003; 26:832–836. [PubMed: 12610045]

8. Lachin JM, McGee P, Palmer JP. Impact of C-peptide preservation on metabolic and clinical outcomes in the Diabetes Control and Complications Trial. *Diabetes*. 2014; 63:739–748. [PubMed: 24089509]
9. Barton FB, Rickels MR, Alejandro R, Hering BJ, Wease S, Naziruddin B, Oberholzer J, Odorico JS, Garfinkel MR, Levy M, Pattou F, Berney T, Secchi A, Messinger S, Senior PA, Maffi P, Posselt A, Stock PG, Kaufman DB, Luo X, Kandeel F, Cagliero E, Turgeon NA, Witkowski P, Naji A, O'Connell PJ, Greenbaum C, Kudva YC, Brayman KL, Aull MJ, Larsen C, Kay TW, Fernandez LA, Vantyghem MC, Bellin M, Shapiro AM. Improvement in outcomes of clinical islet transplantation: 1999–2010. *Diabetes Care*. 2012; 35:1436–1445. [PubMed: 22723582]
10. Vantyghem MC, Raverdy V, Balavoine A-S, Defrance F, Caiazzo R, Arnalsteen L, Gmyr V, Hazzan M, Noel C, Kerr-Conte J, Pattou F. Continuous Glucose Monitoring after Islet Transplantation in Type 1 Diabetes: An Excellent Graft Function (B-score Greater Than 7) Is required to Abrogate Hyperglycemia, Whereas a Minimal Function is Necessary to Suppress Severe Hypoglycemia (B-score Greater Than 3). *J Clin Endocrinol Metab*. 2012; 97:E2078–E2083. [PubMed: 22996144]
11. Keenan HA, Sun JK, Levine J, Doria A, Aiello LP, Eisenbarth G, Bonner-Weir S, King GL. Residual insulin production and pancreatic beta-cell turnover after 50 years of diabetes: Joslin Medalist Study. *Diabetes*. 2010; 59:2846–2853. [PubMed: 20699420]
12. DCCT group. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. The Diabetes Control and Complications Trial Research Group. *N Engl J Med*. 1993; 329:977–986. [PubMed: 8366922]
13. The Diabetes Control and Complications Trial Research Group. Effect of intensive therapy on residual beta-cell function in patients with type 1 diabetes in the diabetes control and complications trial. A randomized, controlled trial. *Ann Intern Med*. 1998; 128:517–523. [PubMed: 9518395]
14. Effect of Intensive Diabetes Therapy on the Progression of Diabetic Retinopathy in Patients With Type 1 Diabetes: 18 Years of Follow-up in the DCCT/EDIC. *Diabetes*. 2015; 64:631–642. [PubMed: 25204977]
15. Thompson DM, Meloche M, Ao Z, Paty B, Keown P, Shapiro RJ, Ho S, Worsley D, Fung M, Meneilly G, Begg I, Al MM, Kondi J, Harris C, Fensom B, Kozak SE, Tong SO, Trinh M, Warnock GL. Reduced progression of diabetic microvascular complications with islet cell transplantation compared with intensive medical therapy. *Transplantation*. 2011; 91:373–378. [PubMed: 21258272]
16. Palmer JP, Fleming GA, Greenbaum CJ, Herold KC, Jansa LD, Kolb H, Lachin JM, Polonsky KS, Pozzilli P, Skyler JS, Steffes MW. C-peptide is the appropriate outcome measure for type 1 diabetes clinical trials to preserve beta-cell function: report of an ADA workshop, 21–22 October 2001. *Diabetes*. 2004; 53:250–264. [PubMed: 14693724]
17. Bergerot I, Fabien N, Maguer V, Thivolet C. Oral administration of human insulin to NOD mice generates CD4+ T cells that suppress adoptive transfer of diabetes. *J Autoimmun*. 1994; 7:655–663. [PubMed: 7840857]
18. Chatenoud L, Primo J, Bach JF. CD3 antibody-induced dominant self tolerance in overtly diabetic NOD mice. *J Immunol*. 1997; 158:2947–2954. [PubMed: 9058834]
19. Chatenoud L, Thervet E, Primo J, Bach JF. Anti-CD3 antibody induces long-term remission of overt autoimmunity in nonobese diabetic mice. *Proc Natl Acad Sci U S A*. 1994; 91:123–127. [PubMed: 8278351]
20. Atkinson M, Maclaren N, Luchetta R. Insulinitis and diabetes in NOD mice reduced by prophylactic insulin therapy. *Diabetes*. 1990; 39:933–937. [PubMed: 2197139]
21. Ben NM, D'Addio F, Uselli V, Tezza S, Abdi R, Fiorina P. The rise, fall, and resurgence of immunotherapy in type 1 diabetes. *Pharmacol Res*. 2014
22. Gottlieb PA, Quinlan S, Krause-Steinrauf H, Greenbaum CJ, Wilson DM, Rodriguez H, Schatz DA, Moran AM, Lachin JM, Skyler JS. Failure to preserve beta-cell function with mycophenolate mofetil and daclizumab combined therapy in patients with new-onset type 1 diabetes. *Diabetes Care*. 2010; 33:826–832. [PubMed: 20067954]
23. Wherrett DK, Bundy B, Becker DJ, DiMeglio LA, Gitelman SE, Goland R, Gottlieb PA, Greenbaum CJ, Herold KC, Marks JB, Monzavi R, Moran A, Orban T, Palmer JP, Raskin P,

- Rodriguez H, Schatz D, Wilson DM, Krischer JP, Skyler JS. Antigen-based therapy with glutamic acid decarboxylase (GAD) vaccine in patients with recent-onset type 1 diabetes: a randomised double-blind trial. *Lancet*. 2011; 378:319–327. [PubMed: 21714999]
24. Moran A, Bundy B, Becker DJ, DiMeglio LA, Gitelman SE, Goland R, Greenbaum CJ, Herold KC, Marks JB, Raskin P, Sanda S, Schatz D, Wherrett DK, Wilson DM, Krischer JP, Skyler JS, Pickersgill L, de KE, Ziegler AG, Boehm B, Badenhop K, Schloot N, Bak JF, Pozzilli P, Mauricio D, Donath MY, Castano L, Wagner A, Lervang HH, Perrild H, Mandrup-Poulsen T, Pociot F, Dinarello CA. Interleukin-1 antagonism in type 1 diabetes of recent onset: two multicentre, randomised, double-blind, placebo-controlled trials. *Lancet*. 2013; 381:1905–1915. [PubMed: 23562090]
 25. Gitelman SE, Gottlieb PA, Rigby MR, Felner EI, Willi SM, Fisher LK, Moran A, Gottschalk M, Moore WV, Pinckney A, Keyes-Elstein L, Aggarwal S, Phippard D, Sayre PH, Ding L, Bluestone JA, Ehlers MR. Antithymocyte globulin treatment for patients with recent-onset type 1 diabetes 12-month results of a randomised, placebo-controlled, phase 2 trial. *Lancet Diabetes Endocrinol*. 2013; 1:306–316. [PubMed: 24622416]
 26. Rigby MR, DiMeglio LA, Rendell MS, Felner EI, Dostou JM, Gitelman SE, Patel CM, Griffin KJ, Tsalikian E, Gottlieb PA, Greenbaum CJ, Sherry NA, Moore WV, Monzavi R, Willi SM, Raskin P, Moran A, Russell WE, Pinckney A, Keyes-Elstein L, Howell M, Aggarwal S, Lim N, Phippard D, Nepom GT, McNamara J, Ehlers MR. Targeting of memory T cells with alefacept in new-onset type 1 diabetes (T1DAL study): 12 month results of a randomised, double-blind, placebo-controlled phase 2 trial. *Lancet Diabetes Endocrinol*. 2013; 1:284–294. [PubMed: 24622414]
 27. Herold KC, Hagopian W, Auger JA, Poumian-Ruiz E, Taylor L, Donaldson D, Gitelman SE, Harlan DM, Xu D, Zivin RA, Bluestone JA. Anti-CD3 monoclonal antibody in new-onset type 1 diabetes mellitus. *N Engl J Med*. 2002; 346:1692–1698. [PubMed: 12037148]
 28. Herold KC, Gitelman SE, Willi SM, Gottlieb PA, Waldron-Lynch F, Devine L, Sherr J, Rosenthal SM, Adi S, Jalaludin MY, Michels AW, Dziura J, Bluestone JA. Teplizumab treatment may improve C-peptide responses in participants with type 1 diabetes after the new-onset period: a randomised controlled trial. *Diabetologia*. 2013; 56:391–400. [PubMed: 23086558]
 29. Herold KC, Gitelman SE, Ehlers MR, Gottlieb PA, Greenbaum CJ, Hagopian W, Boyle KD, Keyes-Elstein L, Aggarwal S, Phippard D, Sayre PH, McNamara J, Bluestone JA. Teplizumab (Anti-CD3 mAb) Treatment Preserves C-Peptide Responses in Patients With New-Onset Type 1 Diabetes in a Randomized Controlled Trial: Metabolic and Immunologic Features at Baseline Identify a Subgroup of Responders. *Diabetes*. 2013; 62:3766–3774. [PubMed: 23835333]
 30. Sherry N, Hagopian W, Ludvigsson J, Jain SM, Wahlen J, Ferry RJ Jr, Bode B, Aronoff S, Holland C, Carlin D, King KL, Wilder RL, Pillemer S, Bonvini E, Johnson S, Stein KE, Koenig S, Herold KC, Daifotis AG. Teplizumab for treatment of type 1 diabetes (Protege study): 1-year results from a randomised, placebo-controlled trial. *Lancet*. 2011; 378:487–497. [PubMed: 21719095]
 31. Hagopian W, Ferry RJ Jr, Sherry N, Carlin D, Bonvini E, Johnson S, Stein KE, Koenig S, Daifotis AG, Herold KC, Ludvigsson J. Teplizumab preserves C-peptide in recent-onset type 1 diabetes: two-year results from the randomized, placebo-controlled Protege trial. *Diabetes*. 2013; 62:3901–3908. [PubMed: 23801579]
 32. Keymeulen B, Vandemeulebroucke E, Ziegler AG, Mathieu C, Kaufman L, Hale G, Gorus F, Goldman M, Walter M, Candon S, Schandene L, Crenier L, De Block C, Seigneurin JM, De Pauw P, Pierard D, Weets I, Rebello P, Bird P, Berrie E, Frewin M, Waldmann H, Bach JF, Pipeleers D, Chatenoud L. Insulin needs after CD3-antibody therapy in new-onset type 1 diabetes. *N Engl J Med*. 2005; 352:2598–2608. [PubMed: 15972866]
 33. Aronson R, Gottlieb PA, Christiansen JS, Donner TW, Bosi E, Bode BW, Pozzilli P. Low-dose oteplizumab anti-CD3 monoclonal antibody DEFEND-1 study: results of the randomized phase III study in recent-onset human type 1 diabetes. *Diabetes Care*. 2014; 37:2746–2754. [PubMed: 25011949]
 34. Pescovitz MD, Greenbaum CJ, Krause-Steinrauf H, Becker DJ, Gitelman SE, Goland R, Gottlieb PA, Marks JB, McGee PF, Moran AM, Raskin P, Rodriguez H, Schatz DA, Wherrett D, Wilson DM, Lachin JM, Skyler JS. Rituximab, B-Lymphocyte Depletion, and Preservation of Beta-Cell Function. *N Engl J Med*. 2009; 361:2143–2152. [PubMed: 19940299]

35. Pescovitz MD, Greenbaum CJ, Bundy B, Becker DJ, Gitelman SE, Goland R, Gottlieb PA, Marks JB, Moran A, Raskin P, Rodriguez H, Schatz DA, Wherrett DK, Wilson DM, Krischer JP, Skyler JS. B-lymphocyte depletion with rituximab and beta-cell function: two-year results. *Diabetes Care*. 2014; 37:453–459. [PubMed: 24026563]
36. Orban T, Bundy B, Becker DJ, DiMeglio LA, Gitelman SE, Goland R, Gottlieb PA, Greenbaum CJ, Marks JB, Monzavi R, Moran A, Raskin P, Rodriguez H, Russell WE, Schatz D, Wherrett D, Wilson DM, Krischer JP, Skyler JS. Co-stimulation modulation with abatacept in patients with recent-onset type 1 diabetes: a randomised, double-blind, placebo-controlled trial. *Lancet*. 2011; 378:412–419. [PubMed: 21719096]
37. Diabetes Prevention Trial Study Group. Effects of insulin in relatives of patients with type 1 diabetes mellitus. *N Engl J Med*. 2002; 346:1685–1691. [PubMed: 12037147]
38. Skyler JS, Krischer JP, Wolfsdorf J, Cowie C, Palmer JP, Greenbaum C, Cuthbertson D, Rafkin-Mervis LE, Chase HP, Leschek E. Effects of oral insulin in relatives of patients with type 1 diabetes: The Diabetes Prevention Trial--Type 1. *Diabetes Care*. 2005; 28:1068–1076. [PubMed: 15855569]
39. Lampeter EF, Klinghammer A, Scherbaum WA, Heinze E, Haastert B, Giani G, Kolb H. The Deutsche Nicotinamide Intervention Study: an attempt to prevent type 1 diabetes. DENIS Group. *Diabetes*. 1998; 47:980–984. [PubMed: 9604880]
40. Gale EA, Bingley PJ, Emmett CL, Collier T. European Nicotinamide Diabetes Intervention Trial (ENDIT): a randomised controlled trial of intervention before the onset of type 1 diabetes. *Lancet*. 2004; 363:925–931. [PubMed: 15043959]
41. Nanto-Salonen K, Kupila A, Simell S, Siljander H, Salonsaari T, Hekkala A, Korhonen S, Erkkola R, Sipila JJ, Haavisto L, Siltala M, Tuominen J, Hakalax J, Hyoty H, Ilonen J, Veijola R, Simell T, Knip M, Simell O. Nasal insulin to prevent type 1 diabetes in children with HLA genotypes and autoantibodies conferring increased risk of disease: a double-blind, randomised controlled trial. *Lancet*. 2008; 372:1746–1755. [PubMed: 18814906]
42. Knip M, Akerblom HK, Becker D, Dosch HM, Dupre J, Fraser W, Howard N, Ilonen J, Krischer JP, Kordonouri O, Lawson ML, Palmer JP, Savilahti E, Vaarala O, Virtanen SM. Hydrolyzed infant formula and early beta-cell autoimmunity: a randomized clinical trial. *JAMA*. 2014; 311:2279–2287. [PubMed: 24915259]
43. Hummel S, Pfluger M, Hummel M, Bonifacio E, Ziegler AG. Primary dietary intervention study to reduce the risk of islet autoimmunity in children at increased risk for type 1 diabetes: the BABYDIET study. *Diabetes Care*. 2011; 34:1301–1305. [PubMed: 21515839]
44. Beyerlein A, Chmiel R, Hummel S, Winkler C, Bonifacio E, Ziegler AG. Timing of gluten introduction and islet autoimmunity in young children: updated results from the BABYDIET study. *Diabetes Care*. 2014; 37:e194–e195. [PubMed: 25147260]
45. Skyler JS. Update on worldwide efforts to prevent type 1 diabetes. *Ann N Y Acad Sci*. 2008; 1150:190–196. [PubMed: 19120293]
46. Noble JA, Valdes AM, Cook M, Klitz W, Thomson G, Erlich HA. The role of HLA class II genes in insulin-dependent diabetes mellitus: molecular analysis of 180 Caucasian, multiplex families. *Am J Hum Genet*. 1996; 59:1134–1148. [PubMed: 8900244]
47. Parikka V, Nanto-Salonen K, Saarinen M, Simell T, Ilonen J, Hyoty H, Veijola R, Knip M, Simell O. Early seroconversion and rapidly increasing autoantibody concentrations predict prepubertal manifestation of type 1 diabetes in children at genetic risk. *Diabetologia*. 2012; 55:1926–1936. [PubMed: 22441569]
48. Ziegler AG, Rewers M, Simell O, Simell T, Lempainen J, Steck A, Winkler C, Ilonen J, Veijola R, Knip M, Bonifacio E, Eisenbarth GS. Seroconversion to multiple islet autoantibodies and risk of progression to diabetes in children. *JAMA*. 2013; 309:2473–2479. [PubMed: 23780460]
49. DPT-1 Study Group. Demographics of relatives screened and ICA positive in the diabetes prevention trial-type 1 diabetes (DPT-1). (Abstract). *Diabetes*. 1997; 46(Suppl 1)
50. Sosenko JM, Skyler JS, Mahon J, Krischer JP, Greenbaum CJ, Rafkin LE, Beam CA, Boulware DC, Matheson D, Cuthbertson D, Herold KC, Eisenbarth G, Palmer JP. Use of the Diabetes Prevention Trial-Type 1 Risk Score (DPTRS) for improving the accuracy of the risk classification of type 1 diabetes. *Diabetes Care*. 2014; 37:979–984. [PubMed: 24550217]

51. Mahon JL, Sosenko JM, Rafkin-Mervis L, Krause-Steinrauf H, Lachin JM, Thompson C, Bingley PJ, Bonifacio E, Palmer JP, Eisenbarth GS, Wolfsdorf J, Skyler JS. The TrialNet Natural History Study of the Development of Type 1 Diabetes: objectives, design, and initial results. *Pediatr Diabetes*. 2009; 10:97–104. [PubMed: 18823409]
52. Greenbaum CJ, Beam CA, Boulware D, Gitelman SE, Gottlieb PA, Herold KC, Lachin JM, McGee P, Palmer JP, Pescovitz MD, Krause-Steinrauf H, Skyler JS, Sosenko JM. Fall in C-peptide during first 2 years from diagnosis: evidence of at least two distinct phases from composite Type 1 Diabetes TrialNet data. *Diabetes*. 2012; 61:2066–2073. [PubMed: 22688329]
53. Buckingham B, Beck RW, Ruedy KJ, Cheng P, Kollman C, Weinzimer SA, DiMeglio LA, Bremer AA, Slover R, Tamborlane WV. Effectiveness of early intensive therapy on beta-cell preservation in type 1 diabetes. *Diabetes Care*. 2013; 36:4030–4035. [PubMed: 24130350]
54. Davis AK, Dubose SN, Haller MJ, Miller KM, DiMeglio LA, Bethin KE, Goland RS, Greenberg EM, Liljenquist DR, Ahmann AJ, Marcovina SM, Peters AL, Beck RW, Greenbaum CJ. Prevalence of Detectable C-peptide According to Age at Diagnosis and Duration of Type 1 Diabetes. *Diabetes Care*. 2014
55. Atkinson MA, Gianani R. The pancreas in human type 1 diabetes: providing new answers to age-old questions. *Curr Opin Endocrinol Diabetes Obes*. 2009; 16:279–285. [PubMed: 19502978]
56. Shah SC, Malone JI, Simpson NE. A randomized trial of intensive insulin therapy in newly diagnosed insulin-dependent diabetes mellitus. *N Engl J Med*. 1989; 320:550–554. [PubMed: 2644534]
57. Greenbaum CJ, McCulloch-Olson M, Chiu HK, Palmer JP, Brooks-Worrell B. Parenteral insulin suppresses T cell proliferation to islet antigens. *Pediatr Diabetes*. 2011; 12:150–155. [PubMed: 20522167]
58. Bunck MC, Diamant M, Corner A, Eliasson B, Malloy JL, Shaginian RM, Deng W, Kendall DM, Taskinen MR, Smith U, Yki-Jarvinen H, Heine RJ. One-year treatment with exenatide improves beta-cell function, compared with insulin glargine, in metformin-treated type 2 diabetic patients: a randomized, controlled trial. *Diabetes Care*. 2009; 32:762–768. [PubMed: 19196887]
59. Chang AM, Jakobsen G, Sturis J, Smith MJ, Bloem CJ, An B, Galecki A, Halter JB. The GLP-1 derivative NN2211 restores beta-cell sensitivity to glucose in type 2 diabetic patients after a single dose. *Diabetes*. 2003; 52:1786–1791. [PubMed: 12829647]
60. Mari A, Degen K, Brock B, Rungby J, Ferrannini E, Schmitz O. Effects of the long-acting human glucagon-like peptide-1 analog liraglutide on beta-cell function in normal living conditions. *Diabetes Care*. 2007; 30:2032–2033. [PubMed: 17468345]
61. Long SA, Rieck M, Sanda S, Bollyky JB, Samuels PL, Goland R, Ahmann A, Rabinovitch A, Aggarwal S, Phippard D, Turka LA, Ehlers MR, Bianchine PJ, Boyle KD, Adah SA, Bluestone JA, Buckner JH, Greenbaum CJ. Rapamycin/IL-2 Combination Therapy in Patients with Type 1 Diabetes Augments Tregs yet Transiently Impairs beta-Cell Function. *Diabetes*. 2012
62. D'Addio F, Valderrama VA, Ben NM, Franek E, Zhu D, Li L, Ning G, Snarski E, Fiorina P. Autologous nonmyeloablative hematopoietic stem cell transplantation in new-onset type 1 diabetes: a multicenter analysis. *Diabetes*. 2014; 63:3041–3046. [PubMed: 24947362]
63. Haller MJ, Gitelman SE, Gottlieb PA, Michels AW, Rosenthal SM, Shuster JJ, Zou B, Brusko TM, Hulme MA, Wasserfall CH, Mathews CE, Atkinson MA, Schatz DA. Anti-thymocyte globulin/G-CSF treatment preserves beta cell function in patients with established type 1 diabetes. *J Clin Invest*. 2014; 125:448–455. [PubMed: 25500887]
64. Haller MJ, Schatz D, Atkinson M. Granulocyte colony stimulating factor (G-CSF) fails to preserve β -cell function in patients with recent onset type 1 diabetes (T1D) (Abstract). *Diabetes*. 2014; 63
65. Cohen SB, Emery P, Greenwald MW, Dougados M, Furie RA, Genovese MC, Keystone EC, Loveless JE, Burmester GR, Cravets MW, Hessey EW, Shaw T, Totoritis MC. Rituximab for rheumatoid arthritis refractory to anti-tumor necrosis factor therapy: Results of a multicenter, randomized, double-blind, placebo-controlled, phase III trial evaluating primary efficacy and safety at twenty-four weeks. *Arthritis Rheum*. 2006; 54:2793–2806. [PubMed: 16947627]
66. Maxwell LJ, Singh JA. Abatacept for rheumatoid arthritis: a Cochrane systematic review. *J Rheumatol*. 2010; 37:234–245. [PubMed: 20080922]

67. Hebert PR, Moser M, Mayer J, Glynn RJ, Hennekens CH. Recent evidence on drug therapy of mild to moderate hypertension and decreased risk of coronary heart disease. *Arch Intern Med*. 1993; 153:578–581. [PubMed: 8439221]
68. Greenbaum CJ, Beam CA, Boulware D, Gitelman SE, Gottlieb PA, Herold KC, Lachin JM, McGee P, Palmer JP, Pescovitz MD, Krause-Steinrauf H, Skyler JS, Sosenko JM. Fall in C-peptide During First 2 Years From Diagnosis: Evidence of at Least Two Distinct Phases From Composite TrialNet Data. *Diabetes*. 2012
69. Ludvigsson J, Carlsson A, Deli A, Forsander G, Ivarsson SA, Kockum I, Lindblad B, Marcus C, Lernmark A, Samuelsson U. Decline of C-peptide during the first year after diagnosis of Type 1 diabetes in children and adolescents. *Diabetes Research and Clinical Practice*. 2013; 100:203–209. [PubMed: 23529064]

Figure 1.
Model-based estimates of average slopes of C-peptide AUC over time according to age quartiles. Greenbaum, et al. Diabetes 2012 (52)

Figure 2.

Proportion of participants with detectable (≥0.017 nmol/L) non-fasting C-peptide, according to age at diagnosis and duration of type 1 diabetes. Davis et al, Diabetes Care, 2014. (54)

Table 1

selected primary and secondary prevention trials in T1D

Study	ENDIT	DENIS	DPT-1	DPT-1	DIP	TRIGR	BABYDIET
Dates	1990–1998	1991–1996	1994–2002	1994–2000	1994–2008	2002–2007	2000–2006
Therapy	nicotinamide	nicotinamide	Oral insulin	Parenteral insulin	Nasal insulin	Casein hydrolysate infant formula	Delayed introduction of gluten in infancy
Primary or secondary	secondary	secondary	secondary	secondary	secondary	primary	primary
Number screened	30,000	2,425	103,391	84,228	116,720	5,606	1,168
Number enrolled	552	68	372	339	224	2160	150
Primary endpoint	Diagnosis of diabetes	Diagnosis of diabetes	Diagnosis of diabetes	Diagnosis of diabetes	Diagnosis of diabetes	2 autoantibodies; diagnosis of diabetes	1 autoantibodies
Outcome	No effect	No effect	No effect overall; post-hoc suggests effect in subgroup with high IAA	No effect	No effect	No effect	No effect
Reference	(40)	(39)	(38)	(37)	(41)	(42)	(43,44)