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Primary and secondary prevention of Type 1 diabetes

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Introduction

Type 1 diabetes is thought to be an immunologically mediated disease, the end result of which is pancreatic islet β-cell destruction [1,2]. Other articles in this review issue address the origins of the disease, including the immunogenotype and the role of environmental factors responsible for initiating the immune response. That initial immune response may engender additional secondary and tertiary responses, which collectively result in impairment of β-cell function, progressive destruction of β-cells and consequent evolution of Type 1 diabetes. This insidious process evolves over a variable amount of time—even many years in some individuals. The eventual overt manifestation of clinical symptoms becomes apparent only when most β-cells have lost function and presumably have been destroyed.

If Type 1 diabetes is an immunologically mediated disease, then immune intervention should alter the natural history of the disease and potentially abrogate the clinical syndrome. The evidence that an immune mechanism may be important in the aetiopathogenesis of human Type 1 diabetes, coupled with the success of immune intervention in animal models, has led to clinical trials of various immune intervention therapies in Type 1 diabetes. Although prevention of Type 1 diabetes is the logical ultimate goal of immune intervention studies, most studies to date have been conducted in recent-onset Type 1 diabetes in an attempt to interdict the disease process and preserve β-cell function. This article will review only prevention studies, undertaken either prior to any evidence of autoimmunity (primary prevention) or after the development of islet autoantibodies (secondary prevention). The goal of such primary and secondary intervention before disease onset is to arrest the immune process and thus prevent or delay clinical disease [3].

Most immunotherapy trials to date have been tertiary prevention trials in individuals with recent-onset Type 1 diabetes. Such subjects are easy to identify. The first immune intervention studies were initiated as early as the late 1970s [4]. Only a few of the early studies in this field were both randomized controlled clinical trials and included sufficient numbers of subjects for there to be valid conclusions [5,6]. Unfortunately, others used either no control subjects, historical comparison groups, or concurrent non-randomized comparison groups. The goal of tertiary intervention trials at or after disease onset is to halt the destruction of remaining β-cells, perhaps allowing these residual β-cells to recover function, hopefully lessening the severity of clinical manifestations and disease progression. A variety of immune interventions have been used, some immunosuppressive and some

Competing interests
The author is chairman of the Type 1 Diabetes Advisory Board of Sanofi Diabetes; serves on advisory boards for Bristol-Myers Squibb, Viacyte and Sekris; has been an advisor to Merck, Gilead and Takeda; and his institution has received research grants from Halozyme, Mesoblast and Osiris.

immunomodulatory. Unfortunately, a lasting clinically beneficial response has not yet been forthcoming [7]. Tertiary intervention studies will not be reviewed here.

It is now recognized that greater emphasis should be placed on primary and secondary prevention trials, in which (1) earlier therapy may better alter the immune processes and (2) greater preserved β-cell mass may improve the likelihood of success. However, such primary and secondary prevention is contingent on effective case finding. For primary prevention, current strategy requires genetic screening at birth and initiation of a trial in those with risk genes. For secondary prevention, current screening strategies include either following a birth cohort with genetic risk until the development of signs of autoimmunity or the screening for autoimmunity amongst high-risk subjects, for example, first-degree relatives of individuals with Type 1 diabetes. Family members of patients with Type 1 diabetes have a 10- to- 20-fold increased risk compared with the general population, and consequently case finding is easier amongst relatives. Trials may then be conducted in those with evidence of autoimmunity.

This review will focus particularly on randomized controlled clinical trials (Table 1).

Primary prevention trials

As primary prevention is directed at individuals with no signs of autoimmunity or metabolic impairment, and uncertainty as to whether they will actually develop Type 1 diabetes, interventions tested must be extremely safe. As a consequence, all primary prevention trials to date have involved dietary interventions designed to interrupt putative environmental triggers of Type 1 diabetes. Unfortunately, as has been stated by Knip *et al.*, ‘so far, no specific dietary factor has been shown to be an unequivocal risk factor for β-cell autoimmunity or Type 1 diabetes, and there are a number of contradictory observations with regard to the effect of various foods’ [8]. As a consequence, a number of different approaches have been proposed or tested.

Dietary interventions

Cow’s milk—Based on epidemiological studies and meta-analyses, which suggested that early introduction of cow’s milk may serve as a trigger of Type 1 diabetes [9,10], a pilot study was initiated in 1995, principally in Finland, evaluating, in babies with high genetic risk markers of Type 1 diabetes, whether at the time of weaning replacement with a formula based on casein hydrolysate rather than cow milk might reduce the development of autoimmunity [11]. The trial randomized 230 infants to receive either a casein hydrolysate formula or a conventional, cow’s-milk formula (control) whenever breast milk was not available during the first 6–8 months of life. Eligible infants had human leukocyte antigen (HLA)-conferred susceptibility to Type 1 diabetes and at least one family member with Type 1 diabetes. Children were followed for 10 years for development of diabetes-related autoantibodies and development of Type 1 diabetes. The investigators reported that the group assigned to casein hydrolysate formula had a reduced risk of development of β-cell autoimmunity (appearance of one or more antibodies) [hazard ratio 0.54 (0.29–0.95) and hazard ratio adjusted for observed difference in duration of exposure to study formula 0.51 (0.28–0.91)] [12].

Given the ability to recruit in the pilot study just reviewed, the investigators then embarked on the ambitious Trial to Reduce Incidence of Diabetes in Genetically at Risk (TRIGR) study, a multinational, randomized prospective trial, to determine whether the frequency of Type 1 diabetes can be reduced by preventing exposure to cow milk proteins early in life (13). The TRIGR study involves 77 centres in 15 countries and registered approximately 5000 newborns and randomized a total of 2160 newborns over a 4.7-year period, completing

enrolment at the end of 2006 [14]. Subjects with the risk HLA genotypes (approximately 45%) were included in the prevention trial, which involves randomization to either casein hydrolysate formula or conventional cow's milk-based formula, with breastfeeding permitted as desired. Planned follow-up is for 10 years for the development of Type 1 diabetes, with expected completion in 2017 when all subjects have reached age 10 years.

Bovine insulin—It has been shown that exposure to bovine insulin in cow's-milk formula has the capacity to induce an immune response to insulin [15]. Therefore, a pilot study, the Finnish Dietary Intervention Trial for the Prevention of Type 1 Diabetes [FINDIA], was initiated, in which the investigators sought to establish whether a formula free of bovine insulin might reduce diabetes autoimmunity. This takes the question one step deeper and specifically removes bovine insulin from infant formula. Again, as in the TRIGR study, eligible infants had HLA-conferred susceptibility to Type 1 diabetes identified on screening. Of 5003 infants screened, 1113 were found eligible, 1104 were randomized and 908 provided at least one follow-up sample. Randomization was to three groups: cow's-milk formula (control), whey-based hydrolysed formula, or whey-based FINDIA formula essentially free of bovine insulin whenever breast milk was not available during the first 6 months of life. Children were followed until age 3 years for the development of diabetes-related autoantibodies. The group assigned to the FINDIA formula had a reduced risk of development of β-cell autoimmunity (appearance of one or more antibodies) [odds ratio in the intention-to-treat analysis 0.39 (0.17–0.91) and in the treatment-received analysis 0.23 (0.08–0.69) ($P < 0.01$) in the FINDIA group when compared with the cow's-milk formula group] [16].

Given the slowing of appearance of autoantibodies in both the Finnish TRIGR Pilot Study and the FINDIA Study, this bodes well for the potential of the full TRIGR Study to have an impact on Type 1 diabetes prevention. Meanwhile, no matter what the outcome of these studies, it would seem prudent to encourage breastfeeding for as long as reasonable. Indeed, the reciprocal of early cow's milk exposure is prolonged breastfeeding, and it could be argued that breastfeeding is protective rather than cow's milk being a precipitant [10].

Gluten—Prospective observational studies suggest that the age at introduction of solid food, such as gluten-containing foods or cereals, affects the development of islet autoimmunity in children who are genetically susceptible to Type 1 diabetes [16,17]. In a pilot study in islet autoantibody-positive children, β-cell function seemed to be improved by deprivation of gluten for 6 months [18]. This led to the BABYDIET study, which was designed to test—in a randomized controlled trial—whether delayed exposure to gluten reduces the risk of diabetes autoimmunity [19]. The trial randomized 150 infants with a first-degree relative with Type 1 diabetes and an HLA genotype consistent with Type 1 diabetes risk. They were assigned either to first gluten exposure at age 6 months (control group) or at age 12 months (late-exposure group) and were followed every 3 months until age 3 years, and yearly thereafter. They were evaluated for safety and appearance of diabetes autoantibodies. Only 70% of subjects followed the protocol, 30% did not. In terms of safety, during the first 3 years, weight and height were similar in children in the control and late-exposure groups. Eleven children in the control group and 13 children in the late-exposure group developed diabetes autoantibodies (3-year risk: 12 vs. 13%; $P = 0.6$). Seven children developed diabetes, including four in the late-exposure group. No significant differences were observed when children were analysed as per protocol on the basis of the reported first gluten exposure of the children. Thus, delaying gluten exposure until the age of 12 months is safe but does not substantially reduce the risk for islet autoimmunity in genetically at-risk children. This is in contract to implications from observational studies, thus emphasizing the importance of randomized controlled clinical trials in answering important questions.

Omega-3 fatty acids—An observational study suggested that dietary intake of omega-3 fatty acids is associated with reduced risk of islet autoimmunity in children at increased genetic risk for Type 1 diabetes [21]. The TrialNet Nutritional Intervention to Prevent (NIP) Type 1 Diabetes Pilot Trial is assessing the feasibility of implementing a full-scale study to determine if nutritional supplements with an omega-3 fatty acid, docosahexaenoic acid (DHA), during the last trimester of pregnancy and the first few years of life, will prevent the development of islet cell autoimmunity in children at high risk for Type 1 diabetes [22]. The hypothesis is that supplementation with DHA will prevent autoantibody development in children at genetic risk for Type 1 diabetes. The NIP Diabetes Pilot is a multi-centre, two-arm, randomized, double-masked, placebo-controlled clinical trial. There are two entry pathways for study participants: (1) pregnant mothers are randomized after the 24th week of pregnancy to take either DHA or placebo study capsules. At birth, or soon after, their babies are tested for HLA type. If the HLA typing shows the baby is at risk for Type 1 diabetes, they will then continue in the study on either DHA or placebo; [2] babies who are deemed eligible upon HLA testing are entered directly up until 6 months of age. They receive either standard formula or DHA-supplemented formula. The pilot trial has been completed although not yet published. During the relatively brief follow-up, there was no change in islet autoimmunity although other variables suggested that this approach should be studied further.

Vitamin D—Vitamin D has been shown to prevent insulitis and Type 1 diabetes in several mouse models of Type 1 diabetes [23]. Vitamin D supplementation in early childhood may offer protection against the development of Type 1 diabetes. Several retrospective studies found beneficial effects of supplementation with regular vitamin D in early life on the later lifetime risk of Type 1 diabetes [23]. However, a recent analysis from the prospective Diabetes Autoimmunity Study in the Young (DAISY) Study found that neither vitamin D intake nor 25(OH)-vitamin D levels throughout childhood were associated with the risk of islet autoimmunity or progression to Type 1 diabetes [24]. A meta-analysis of data from four case–control studies and one cohort study revealed lately that the risk of Type 1 diabetes was significantly reduced (29% reduction) in infants who were supplemented with vitamin D as compared with those who were not supplemented (pooled odds ratio 0.71, 95% CI 0.60–0.84) [25]. Controlled trials with vitamin D have been conducted in new-onset Type 1 diabetes and have shown mixed results, with one showing benefit [26] and two others failing to do so [27,28]. What is needed are adequately powered, randomized controlled trials with long periods of follow-up. To that end, it has been shown that it is possible to recruit babies from the general population for identification of HLA-associated risk status followed by enrolment by 1 month of age to a randomized controlled prevention trial of vitamin D supplementation [29]. These investigators have proposed a nationwide study in Canada to test the hypothesis that vitamin D supplementation can decrease the risk of islet autoimmunity and Type 1 diabetes.

Primary prevention summary

In summary, for primary prevention of Type 1 diabetes, it is necessary to conduct studies in infancy prior to the development of islet autoantibodies. Until evidence of both safety and effectiveness emerges, such studies should be confined to individuals with high-risk genetic markers. Most such studies have involved dietary manipulation or supplementation. Further studies are needed to clarify what dietary components are best altered in attempts at primary prevention of Type 1 diabetes. It also could be argued that it might be appropriate to test vaccines for primary prevention—either vaccines against putative viral or other infectious triggers, or antigen-specific vaccines. To date, no such studies have been initiated.

Secondary prevention trials

Nicotinamide

Nicotinamide is a water-soluble vitamin (B6) derived from nicotinic acid. In animal models of spontaneous and induced diabetes, nicotinamide has been shown to increase insulin synthesis and, if administered before onset, to prevent development of diabetes. As long ago as 1947, nicotinamide was shown to inhibit the development of diabetes in alloxan-treated rats [30]. It was subsequently found to be effective in preventing streptozotocin-induced diabetes [31] and to prevent the spontaneous development of diabetes in the non-obese diabetic (NOD) mouse [32].

An interesting prevention study with nicotinamide was conducted in 1988–1991 in Auckland, New Zealand [33]. In this study, school children age 5–8 years (with no immediate family history of diabetes) were randomized by school to receive islet cell antibody (ICA) testing. A total of 33 658 children were offered testing; 20 195 accepted and 13 463 declined. From those tested, on the basis of either ICA levels of ≥ 10 Juvenile Diabetes Foundation (JDF) units and first-phase insulin release < 25th percentile of normal, or those with ICA > 20 JDF units, 150 children were treated with nicotinamide (maximum dose 1.5 g/day). Another 48 335 children were neither screened nor treated, and served as controls. The rate of development of Type 1 diabetes was $8.1/10^5$ per year in the nicotinamide-treated group vs. $20.1/10^5$ per year in the comparison group ($P = 0.03$). The rate in those who refused testing was $15.1/10^5$ per year. No adverse effects were seen in treated subjects.

Two large multi-centre randomized, double-masked, controlled clinical trials evaluated the effects of nicotinamide in at-risk relatives of individuals with Type 1 diabetes.

The German (Deutsch) Nicotinamide Diabetes Intervention Study (DENIS) identified siblings (age 3–12 years) of patients with Type 1 diabetes thought to be of risk of developing Type 1 diabetes within 3 years [34]. They randomized 55 subjects to either high-dose nicotinamide-slow release (1.2 g m^{-2} day^{-1}) or placebo. They were followed prospectively in a controlled trial using a sequential design. The rate of development of Type 1 diabetes was similar in both groups throughout the observation period (maximum 3.8 years, median 2.1 years). This sequential design provides a 10% probability of a type II error against a reduction of the cumulative diabetes incidence at 3 years from 30 to 6% by nicotinamide. The trial was terminated when the second sequential interim analysis after the eleventh case of diabetes showed that the trial had failed to detect a reduction of the cumulative diabetes incidence at 3 years from 30 to 6% ($P = 0.97$).

The European Nicotinamide Diabetes Intervention Trial (ENDIT) was a prospective, placebo-controlled, double-masked international trial [35]. ENDIT recruited ICA-positive, first-degree relatives (5–40 years old) of individuals with Type 1 diabetes that had onset at less than 20 years of age [35]. These individuals had a projected 5-year risk of Type 1 diabetes of 40%. The study randomized 552 participants either to nicotinamide (1.2 g m^{-2} day^{-1}) or placebo. To identify eligible subjects, ENDIT screened 35 000 first-degree relatives. After approximately 4 years of follow-up, the rate of development of Type 1 diabetes was nearly identical in both the nicotinamide and placebo groups, with an unadjusted hazard ratio for the development of Type 1 diabetes of 1.07 (95% CI 0.78–1.45; $P = 0.69$) and a hazard ratio adjusted for baseline age, glucose tolerance and number of islet autoantibodies of 1.01 (95% CI 0.73–1.38; $P = 0.97$) [35]. Thus, nicotinamide did not prevent or delay development of Type 1 diabetes.

Antigen-specific therapy

Antigen-specific therapy is the holy grail of immunotherapy for prevention of Type 1 diabetes [36]. The concept is that appropriate administration of a diabetes autoantigen has the potential to control the autoimmune response by diverting the immune system to a protective rather than destructive response, and potentially even to induce or restore tolerance. Moreover, the use of antigens is presumably quite safe, they are specific for Type 1 diabetes and are not expected to alter generalized immune responses. Mucosal administration of antigen (oral or intranasal) is particularly thought to favour protective immunity over destructive immunity, and thus has been the route used in several trials.

Insulin

As insulin is the most clear β-cell-specific antigen, several studies have attempted interventions with insulin by a variety of routes.

The Diabetes Prevention Trial-Type 1 (DPT-1) Study Group conducted two studies concomitantly, evaluating injected or parenteral insulin in individuals with a projected 5-year risk of at least 50% [37] and oral insulin in individuals with a projected 5-year risk of 25–50% [38]. These studies randomized 339 and 372 subjects, respectively, in both trials, with an intervention to control ratio of 1:1. However, to identify those 711 eligible and randomized subjects, over 100 000 relatives of Type 1 diabetes patients were screened [38].

The DPT-1 parenteral insulin trial tested not only whether insulin as an antigen could modulate immunity, but also whether insulin use might result in ‘β-cell rest’, thus decreasing presentation of antigen to the immune system [37]. Subjects had islet cell antibodies and either reduced first-phase insulin response to intravenous glucose or glucose intolerance during an oral glucose tolerance test. The intervention used was twice-daily injections of long-acting ultralente insulin (total daily dose of 0.25 units/kg), plus a 96-h continuous intravenous insulin infusion at baseline and annually thereafter. The control group was ‘close observation’ without either placebo injections or placebo infusions. Unfortunately, the rate of development of diabetes was the same in both the treated group and the control group. Importantly, 5-year rate of developing Type 1 diabetes indeed was greater than 50%—in fact both groups had an approximately 65% rate of Type 1 diabetes over 5 years.

A study conducted by The Belgian Diabetes Registry also evaluated whether parenteral insulin might delay the development of Type 1 diabetes [39]. In this study, regular insulin was administered twice daily before the most carbohydrate-rich meals, the concept being that would better induce ‘β-cell rest’ than the long-acting insulin used in the DPT-1 trial. This study also used a close observation control group, randomizing 25 subjects each to treatment and control. Subjects were age 5–40 years, with IA-2 antibodies and normal oral glucose tolerance. There was no difference in rate of progression to Type 1 diabetes.

The DPT-1 oral insulin trial was a randomized, placebo-controlled clinical trial, testing whether mucosal delivery of insulin might result in protective immunity slowing development of Type 1 diabetes [38]. Subjects had both islet cell antibodies and insulin autoantibodies (IAA), intact first-phase insulin response to intravenous glucose and normal glucose intolerance. Oral insulin (7.5 mg of insulin crystals) or matched placebo could either be swallowed as a capsule or the capsule opened and the contents sprinkled on food. Unfortunately, the rate of development of diabetes was the same in the both the oral insulin group and the placebo group. Importantly, 5-year rate of developing Type 1 diabetes indeed was 25–50%—in fact both groups had an approximately 35% rate of Type 1 diabetes over 5 years. However, a subgroup was identified, in a post-hoc analysis, that appeared to show a

beneficial effect of oral insulin [3,38]. That subgroup included individuals with higher titres of insulin autoantibodies at the time of enrolment. In that subgroup, there was a projected delay of 4.5–5 years in onset of Type 1 diabetes in subjects with a confirmed baseline IAA titre over 80 nU/ml [38] and a projected 10-year delay in individuals with a confirmed baseline IAA titre over 300 nU/ml [3]. Long-term follow-up of the DPT-1 oral insulin cohort showed that, even after administration of oral insulin was ceased, effects were maintained [40]. Therefore, Type 1 Diabetes TrialNet, a clinical trials network [41], is conducting another oral insulin trial in subjects with similar characteristics of those in the subgroup with higher titre IAA [42].

The Type 1 Diabetes Prediction and Prevention (DIPP) study was conducted in Finland amongst newborns from the general population (i.e. without relatives) with high risk HLA-DQB1 susceptibility alleles for Type 1 diabetes [43]. The DIPP study screened cord blood samples of 116 720 consecutively born infants and identified 17 397 (~15%) with high or moderate genetic risk, of whom 10 577 participated in a prospective study in which there was serial analysis for diabetes autoantibodies. Of these, 328 met the enrolment criteria of ≥ 2 antibodies in at least two consecutive samples, and 224 were randomized to receive either intranasal insulin (1 unit/kg body weight daily) or placebo in a double-masked controlled clinical trial. The DIPP study also screened 3430 siblings of those infants with increased risk and found that 1613 (~47%) also had increased risk alleles, of whom 1423 participated in prospective follow-up. Of siblings, 52 met the enrolment criteria of ≥ 2 antibodies in at least two consecutive samples, and 40 were randomized to receive nasal insulin or placebo. Unfortunately, within each of the two cohorts (infants and siblings), the rate of progression to Type 1 diabetes was the same in the nasal insulin group and the placebo group.

The Intranasal Insulin Trial (INIT 1) was designed to test safety of intranasal insulin [44]. Using a double-blind crossover design, 38 subjects at risk of Type 1 diabetes, median age 10.8 years (range 5–33 years), with diabetes autoantibodies, were enrolled. They were treated with either intranasal insulin spray or placebo, daily for 10 days, and then 2 days a week for 6 months, after which they were crossed over to the other treatment.. The trial showed that intranasal insulin does not accelerate the onset of diabetes. There did not appear to be acceleration of onset of Type 1 diabetes or other adverse outcomes. Intranasal insulin was associated with an increase in antibody and a decrease in T-cell responses to insulin, changes consistent with mucosal tolerance to insulin. This was also suggested in a subsequent study of nasal insulin in patients with Type 1 diabetes, in whom the interferon-γ response of blood T-cells to proinsulin was suppressed after nasal insulin [45].

The Intranasal Insulin Trial (INIT II) began in late 2006, under the auspices of the Diabetes Vaccine Development Centre (DVDC), an Australian non-profit organization [46]. This is a randomized, double-blind, placebo-controlled multi-centre clinical trial, which will determine whether intranasal insulin can delay or prevent the onset of Type 1 diabetes in children and young adults who are antibody-positive relatives of individuals with Type 1 diabetes at risk of the disease. The trial expects to enrol 300 subjects, age 4 to 30 years, who have two or more diabetes autoantibodies and a normal response in an oral glucose tolerance test.

The PrePoint study is a primary prevention pilot study (mentioned here rather than earlier to place it in context of mucosal use of antigen) evaluating oral or nasal insulin in very high-risk children with genetic markers, to determine whether this might prevent the emergence of islet autoantibodies [47].

Proinsulin peptide(s)

Another antigen-based approach that could be used for prevention is the intradermal administration of a proinsulin peptide, or a cocktail of proinsulin peptides. A pilot safety study with a single proinsulin peptide has been conducted in individuals with established Type 1 diabetes [48]. The peptides selected are those with epitopes recognized by HLA-DR4. Appropriate enabling studies for a potential trial with several proinsulin peptides are currently underway.

Glutamic acid gecarboxylase

Another antigen that is being tested as an antigen-specific therapy is glutamic acid decarboxylase (GAD). The DIAPREV-IT (Diabetes Prevention—Immune Tolerance) Study is being conducted in Southern Sweden, assessing whether a vaccine using GAD with an aluminum hydroxide (alum) adjuvant can prevent Type 1 diabetes [49]. This 50-subject double-masked randomized controlled clinical trial is fully enrolled. Eligible children are 4 years or older, have positive GAD antibodies and at least one additional autoantibody and not yet Type 1 diabetes.

Immunomodulation

A French pilot trial studied whether immunosuppression with low-dose cyclosporine in first-degree relatives of patients with Type 1 diabetes with islet cell antibodies, reduced first-phase insulin response and impaired glucose tolerance [50]. Cyclosporine was given at an initial dose of 7.5 mg kg^{-1} day^{-1} and tapered after the end of the first year. Six cyclosporine-treated subjects were compared with nine historical controls. All of the controls developed Type 1 diabetes within 12 months, whereas two of the cyclosporine-treated subjects remained without Type 1 diabetes 47 and 57 months after initiation of cyclosporine. This tiny study suggested that immunomodulation may be beneficial in delaying progression to Type 1 diabetes.

Currently, Type 1 Diabetes TrialNet is conducting a randomized placebo-controlled trial with the anti-CD3 monoclonal antibody teplizumab to determine whether this form of immunomodulation can delay or prevent frank Type 1 diabetes in relatives at high risk of Type 1 diabetes [51]. Enrolment criteria include two diabetes autoantibodies and having dysglycaemia (a glucose abnormality) during an oral glucose tolerance test, but not yet meeting the criteria for diagnosis of Type 1 diabetes. Enrolment is in progress.

Type 1 Diabetes TrialNet also has just embarked on a randomized placebo-controlled trial with the co-stimulation blocker abatacept to determine whether this can delay or prevent Type 1 diabetes in relatives at risk of Type 1 diabetes [52]. Enrolment criteria include two diabetes autoantibodies and a normal oral glucose tolerance test. Enrolment has recently begun.

Secondary prevention summary

In summary, for secondary prevention of Type 1 diabetes, a number of interventions have been tested and more are currently under evaluation. Unfortunately, no study to date has shown delay or prevention of Type 1 diabetes in the primary analysis, although post-hoc analyses of the DPT-1 oral insulin trial did identify a subgroup with apparent benefit, as discussed above [3,38]. Yet, all completed controlled trials have used benign interventions —nicotinamide or insulin. Studies currently underway are using immunomodulatory agents that have been shown to have some beneficial effect in recent-onset Type 1 diabetes. However, these are still enrolling and no results are available.

Conclusions

Based on our current concepts of the immunopathogenesis of Type 1 diabetes [1,2], it should be possible to delay or prevent the disease. Unfortunately, to date, for both primary and secondary prevention studies there has not been unambiguous evidence of clinical benefit from any intervention tested. Amongst primary prevention studies, elimination of cow's milk proteins in infant formula in the Finish TRIGR pilot study [11] and elimination of bovine insulin in infant formula in the FINDIA study [15], did result in a reduction of formation of islet autoantibodies. Amongst secondary prevention studies, the only evidence of delay of Type 1 diabetes comes from a subgroup identified by post-hoc analyses of the DPT-1 oral insulin trial [3,38]. The results from the Finish TRIGR pilot are being further studied in the full TRIGR trial [13], which is fully enrolled and should report its primary outcome around 2017. The results from the post-hoc analyses of the DPT-1 oral insulin trial also are being further studied in the TrialNet oral insulin trial [42], which is still enrolling subjects. Thus, the intriguing data from the Finish TRIGR pilot and the DPT-1 oral insulin trial will be confirmed or refuted by rigorous trials.

Although not reviewed here, some tertiary intervention trials (at or after disease onset) have shown at least transient benefit in preserving β-cell as measured by C-peptide [2,7,53]. Yet, taming the immune response seems to be a difficult task. To be successful, some combination of intervention strategies may be necessary [53].

As for directions in primary and secondary prevention, safety concerns have heretofore limited the number of approaches taken. To be successful, it may be that one needs to look at an appropriate balance of safety, potential efficacy and the impact of Type 1 diabetes if no action is taken. This likely will mean use of vaccines—antigen-specific vaccines or vaccines against putative infectious triggers—for primary prevention. For secondary prevention, depending on projected risk of Type 1 diabetes, evaluation of immunomodulatory agents is likely to expand.

The field is ripe for more prevention trials. My bias is that progress is being made, albeit more slowly than we might have hoped. Ultimately, we will be able to stop Type 1 diabetes [53].

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Table 1

Randomized controlled prevention trials

Study	Number randomized	Age range	1°Outcome	*P*-value	Reference no.
Primary prevention studies					
Finnish TRIGR pilot	230	Birth	Autoantibodies	0.005	11
TRIGR	2160	Birth	Diagnosis of Type 1 diabetes	*	13
FINDIA	1104	Birth	Autoantibodies	0.01	15
BABYDIET	150	Birth	Autoantibodies	NS	20
NIP	123	Birth	Pilot study	__ †	22
Secondary prevention studies					
DENIS	55	3–12 years	Diagnosis of Type 1 diabetes	NS	34
ENDIT	552	3–40 years	Diagnosis of Type 1 diabetes	NS	35
DPT-1 Parenteral Insulin	339	4–45 years	Diagnosis of Type 1 diabetes	NS	37
Belgian Parenteral Insulin	50	5–40 years	Diagnosis of Type 1 diabetes	NS	39
DPT-1 Oral insulin	372	3–45 years	Diagnosis of Type 1 diabetes	NS	38
TrialNet Oral insulin	Enrolling	3–45 years	Diagnosis of Type 1 diabetes	*	42
DIPP birth cohort	224	1–5 years	Diagnosis of Type 1 diabetes	NS	43
DIPP sibling cohort	40	4–11 years	Diagnosis of Type 1 diabetes	NS	43
INIT-1	38	5–33 years	Safety	NS	44
INIT-II	Enrolling	4–20 years	Diagnosis of Type 1 diabetes	*	46
DIAPREV-IT	50	4–18 years	Diagnosis of Type 1 diabetes	*	49
Trial Net Teplizumab (to date)	Enrolling	8–45 years	Diagnosis of Type 1 diabetes	*	51

Study	Number randomized	Age range	1°Outcome	*P*-value	Reference no.
TrialNet Abatacept	Enrolling	6–45 years	Diagnosis of Type 1 diabetes	*	52

*Data not yet available.

†Randomized pilot study.

NS, not significant.