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PREVENTION OF TYPE 1A DIABETES

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Abstract

Objective—Review prediction of Type 1 diabetes in light of current trials for prevention and preclinical novel therapist.

Methods—We estimate from islet autoantibody testing of random cadaveric donors that approximately ½ million individuals in the United States express multiple islet autoantibodies and are developing Type 1A (immune mediated) diabetes. It is now possible to predict not only risk for Type 1A diabetes but also the approximate age of diabetes onset of children followed from birth.

Results—In animal models diabetes can be prevented and some of the immunologic therapies effective in animal models are able to delay loss of insulin secretion in man.

Conclusion—Unfortunately none of the therapies studied to date in man can completely arrest progressive loss of insulin secretion from destruction of islet beta cells. Nevertheless current knowledge of pathogenesis (targeting trimolecular recognition complex: MHC- peptide- T cell receptor) and natural history combined with newer diagnostic methods allows accurate diagnosis and has stimulated the search for novel safe and effective preventive therapies.

Keywords

Islet; autoantibody; diabetes; beta cells

STAGES IN THE DEVELOPMENT OF TYPE 1A DIABETES

Following the discovery of cytoplasmic islet cell antibodies by Botazzo and Doniach in 1974(1) and studies of monozygotic twins(2), in 1986 we proposed a model of the development of Type 1A diabetes as a chronic autoimmune disorder that could be divided into stages beginning with genetic susceptibility, followed by triggering of autoimmunity marked by the appearance of islet autoantibodies followed by progressive loss of islet beta cells with subsequent metabolic abnormalities and then overt hyperglycemia and essentially complete loss of islet beta cells(3) (Figure 1). The model has stood the test of time with enhancements related to the development of improved assays for islet autoantibodies(4-7) and C-peptide(8), defining genetic loci underlying diabetes risk(9), definition of multiple methods to define progressive loss of beta cell function(10), and better understanding of Type 1 diabetes pancreatic pathology(11). The slowly progressive course of autoimmune diabetes is almost certainly due to lobular non-synchronous destruction of islet beta cells

creating over time more and more pseudoatrophic islets (islets lacking all beta cells (insulin producing islet cells) but retaining islet cells producing glucagon, somatostatin, and pancreatic polypeptide)(12). In the major NOD mouse model of autoimmune diabetes, insulin is the primary autoantigen, as evidenced by the ability to prevent essentially all diabetes by mutating a single amino acid of insulin(13;14). It is very likely that insulin is also the primary target in man given the specific beta cell destruction (non-beta islet cells express GAD, IA-2, and ZnT8). The levels of insulin autoantibodies correlate with the rate of progression to diabetes(15) and a polymorphism of the human insulin gene is the second most important genetic determinant of Type 1 diabetes(16;17). The protective variant of the insulin gene is associated with increased expression of insulin in the thymus, likely leading to deletion of thymic autoreactive T cells targeting insulin. Insulin autoantibodies are almost always the first autoantibody to appear in children followed from birth to Type 1 diabetes(18), but of note the levels of insulin autoantibodies vary over the years prior to diabetes, suggesting that the rate of islet beta cell destruction may well vary over time (since mean levels correlate with rate of progression to diabetes(15)). With sensitive assays for C-peptide (C-peptide is secreted by beta cells in a 1:1 ratio with insulin) approximately 10% of patients with long-term Type 1 diabetes retain some insulin secreting cells(8) (concordant with pathology)(19) while approximately 2% may retain physiologically significant insulin secretion. Rare individuals even after 50 years of Type 1 diabetes have areas of the pancreas that appear normal, with other areas with complete islet beta cell destruction(19). Dr. Atkinson in Gainesville heads the JDRF sponsored nPOD program (website JDRFnPod) with on-line slides of pancreas sections obtained from cadaveric donors with type 1 diabetes of varied duration as well as cadaveric donors without diabetes with expression of multiple autoantibodies. Pancreas of multiple islet autoantibody positive cadaveric donors can have both insulinitis and areas of pseudoatrophic islets consistent with chronic progressive immune mediated beta cell destruction(20).

Given current knowledge of the natural history of Type 1A diabetes it is possible to design trials for prevention at each of the stages of the disorder. The major genetic determinant of Type 1A diabetes are HLA alleles(9;21). In particular the highest risk Type 1A diabetes genotype (consists of heterozygous individuals with DR3-DQ2 and DR4-DQ8) has a risk approaching 5%. Approximately 30% of patients with Type 1A diabetes have this genotype compared to 2% of the general U.S. population. In that DQ, DR, DP and HLA class I alleles can readily be measured and influence risk trials in genetically at risk individuals are underway (e.g. Bonifacio Prepoint study) in individuals lacking islet autoantibodies but predicted to have a 50% risk of activating islet autoimmunity(22-25). There are now four major biochemically defined islet autoantibodies (autoantibodies to insulin, glutamic acid decarboxylates (GAD), insulinoma associated antigen (IA-2), and the islet zinc transporter (ZnT8). Commercial assays are now available for each of these autoantibodies. Expression of ≥ 2 of these four autoantibodies (with high specificity assays= i.e. $\leq 1/100$ controls positive for each autoantibody) in children followed from birth is associated with 90% development of diabetes by 10 years and with the diabetes trend suggesting that with more time the risk might rise to 100%(26;27). Thus trials post-autoantibody expression are feasible(28) and conceptually analogous to the treatment of chronic active hepatitis prior to cirrhosis.

In an individual with characteristic Type 1 diabetes (e.g. childhood onset, non-obese) a single autoantibody is usually sufficient to confirm diagnosis of Type 1A diabetes. There are two major caveats. Insulin autoantibodies can develop post-insulin injection in non-autoimmune diabetes patients. Islet autoantibodies are lost with time, though approximately 50% of patients with Type 1A diabetes can retain islet autoantibodies for decades. Expression of multiple (≥ 2) islet autoantibodies (of insulin, GAD65, IA-2, or ZnT8) in an individual with diabetes is essentially diagnostic of Type 1A or autoimmune diabetes. Relying on multiple autoantibodies for diagnosis rather than a single islet autoantibody is especially important for patients with a clinical diagnosis of Type 2 diabetes. In questionable patients, HLA DR and DQ typing can aid in diagnosis but such typing is not definitive. For example the allele DQB1*0602 is highly protective for type 1A diabetes as it is found in 20% of general U.S. population but only 1% of children with autoantibody positive Type 1A diabetes.

Lack of islet autoantibodies can also be informative. More than 90% of children with new onset diabetes express one or more of the four major islet autoantibodies. An onset child lacking all four of the islet autoantibodies has a 10% risk of monogenic forms of diabetes(29). The child's prognosis depends on the specific mutated gene with some disorders worse than Type 1A diabetes (e.g. Wolfram syndrome) and some allowing treatment with oral hypoglycemic agents (HNF-4) or no treatment at all (glucokinase heterozygous mutations). Approximately 1/2 of African American and Hispanic American children lack islet autoantibodies and a major subset of these have a non-autoimmune form of diabetes where beta cells per islet are lost (Pathology Pattern B) and there are no pseudoatrophic islets (Pathology Pattern A)(11).

STATUS OF TRIALS

A very large number of therapies have failed to influence loss of beta cell function despite ability to prevent diabetes in autoimmune animal models(30). This includes nicotinamide, low-dose subcutaneous insulin, immunization with the antigen GAD in alum(31), the immunostimulant BCG vaccine(32), and oral or nasal insulin (to induce mucosal tolerance) (33). A subset of subjects with high levels of insulin autoantibodies receiving oral insulin in the DPT NIH prevention study appeared to have significant protection, (for the highest level of insulin autoantibodies as much as a seven year delay). A Trialnet study is underway to determine if such protection can be confirmed(28).

There are also several studies with documented delay of loss of beta cell function in trials at the onset of Type 1 diabetes. This includes studies utilizing cytoxan combined with anti-thymocyte globulin(34;35), anti-CD3(36) and anti-CD20(37) monoclonal antibodies, and CTLA-4IG(38). The most dramatic effects were seen in the Brazilian study of Cytoxan and anti-thymocyte globulin and GCSF, with the majority of the patients able to discontinue insulin and a subset off insulin for several years(34). This study was relatively small and lacked a placebo control group, with a concern that a subset of individuals might not have Type 1A diabetes. An obvious major concern is the utilization of relatively high dose cytoxan. Studies of anti-thymocyte globulin (ATG) and GCSF combined with ATG without cytoxan are underway. None of the other therapies delaying loss of C-peptide secretion had

as dramatic an effect, potentially related to less effective immunosuppression. The chronic loss of beta cell function post-diabetes onset was typically delayed for 6 months to one year and then progressive loss resumed that paralleled loss of the placebo groups(39). It is noteworthy that the C-peptide curves were similar with multiple very different therapies. For instance the anti-CD3 antibodies are hypothesized to act by inducing regulatory tolerance(40) while the anti-CD20 antibodies dramatically deplete B-lymphocytes and both only delayed progressive loss of C-peptide secretion. To date the phase III trials of anti-CD3 antibodies have been disappointing in terms of not meeting clinical endpoints (e.g. HbA1c) despite multiple trials decreasing loss of C-peptide. This may relate to inadequate dosing and/or trial designs (e.g. HbA1c as endpoint with intensive insulin therapy in short-term diabetics, subjects from diverse countries mixed together). It may take combination therapy to impact progressive beta cell loss and such trials are planned(41).

CONCLUSION

I believe the status of current trials for the prevention of Type 1A diabetes (which includes trials preventing loss of beta cell function post-onset) suggest that altering the chronic progressive autoimmune killing of beta cells will not be “safely” achieved with broad targeting of the immune system. In addition, current insulin therapy of Type 1A diabetes is improving, particularly with development of continuous glucose monitoring devices that can turn off insulin pumps to limit severe hypoglycemia. This raises the bar for the safety of preventive immunologic therapies.

My epidemiology colleagues believe that the best prevention of Type 1A diabetes will come from elimination of triggering factors. For instance a large trial of removing cow's milk from the diet of infants is underway(42). Unfortunately triggering factors given the high risk for identical twins(43) are likely to be ubiquitous or potentially stochastic and have proven difficulty to identify. Nevertheless environmental factors influencing development of Type 1A diabetes certainly exist and are changing with the doubling of Type 1A diabetes incidence every 20 years(44).

For the prevention of Type 1A diabetes we are left with the need to better understand the specific molecular pathogenesis and to develop specifically targeted therapies. I believe therapies inducing tolerance to islet antigens or interrupting antigen presentation by specific HLA allele are most likely to lead to safe prevention.

The importance of regulatory T cells for the human immune system is undoubted(45). Children with mutations of the FoxP3 gene controlling development of a major subset of such T cells (IPEX syndrome) develop Type 1A diabetes in the first weeks of life (something essentially never seen in typical Type 1A diabetes).

Our studies have been pursuing small molecules that bind in the groove of specific MHC alleles. Blocking or enhancing presentation of target peptides (e.g. a fragment of insulin (B: 9-23)) can prevent diabetes of NOD mice(46). Having molecular structures of relevant trimolecular complexes (target peptide, presenting MHC molecule and T cell receptors) recognizing the target peptide in specific MHC registers(47), can be utilized to design drugs

to prevent diabetes. In rat models of type 1A diabetes a monoclonal antibody to germline encoded T cell receptor sequence (Vbeta 13) prevents diabetes(48).

At present for no autoimmune disorder is there an effective and safe antigen specific immunologic therapy. Thus it should be kept in mind that the field of the immunology of diabetes is pursuing what is currently impossible in man (though possible in animal models) and that success would likely have wide impact on multiple immunologic disorders.

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“Stages” in Development of Type 1A Diabetes

Figure.

Stages Model of development of Type 1A (autoimmune) diabetes as a chronic autoimmune disorder with variation in the rate of beta cells destruction during progression to hyperglycemia when approximately 80% of islet beta cells (insulin secreting cells of the pancreas) have been destroyed.