Type 1 diabetes research: Newer approaches and exciting developments

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Dr. O. Raha and others[1] have written an extensive and exhaustive report on type 1 diabetes (TID) research. They have addressed the role of genetics, environment, bio-markers as well as prevention.

In this Editorial I would like to bring to the attention of readers three important aspects of TID research in the area of TID incidence, role of viruses and some new approaches taken by the Type 1 Diabetes Genetics Consortium (T1DGC). I would further like to discuss current approaches in beta cell preservation and regeneration of new beta cells that are likely to benefit not only newly diagnosed TID patients but also those who developed TID in the past.

A recent report published in Lancet[2] indicates that TID incidence has doubled and is likely to double from now to year 2020 in those aged below five years and increase 70% in those below 15 years. There is an annual increase in incidence in each of the countries studied in Europe and a trend towards an increase among younger children. Interestingly, lower incidence countries in Eastern Europe have seen a rapid increase in yearly incidence (eg: Romania and Poland). This increase in incidence cannot be attributed to the changing genetic makeup of the population. What is changing is the lifestyle and practice of better hygiene. Environment and lifestyle seem to be changing and this is most likely the cause for increase. The reasons attributed for the increase in European population, based on the analytical epidemiological studies, are (i) modern lifestyle habits (ii) increased height and weight development (iii) increased caesarean section deliveries or (iv) reduced frequency of early infections. The Eastern Europe is actually playing catch-up with Western Europe and the increased incidence also correlates with increased Gross Domestic Product (GDP) of those countries. This becomes highly relevant for Indian scenario as India is in a similar situation.

The National Institute of Health (NIH) is pioneering some of the world-wide efforts in TID genetic studies under the TIDGC. More information on this can be found on the website: www.t1dgc.org where one can find the latest in the Genome Wide Association Studies (GWAS) from TID samples collected from all over the world. This effort has resulted in the identification of 40 new loci[3] for TID. This is in addition to the four known non-HLA loci (INS, CTLA4, PTPN22 and IL-2RA). Off all the loci, association of HLA stands out as the only locus with highest lod scores whereas the rest come close to 1.5 to two. The DNA or data from the TIDGC is available for researchers worldwide to perform more studies and more data analysis to come up with newer findings. A new database for TID research has been setup in this initiative called ‘TIDbase’ where one can find a lot of information and cross references (www.t1dbase.org).

Viruses are major players under environmental factors implicated in the etiology of the disease. A recent report in the May 28 issue of Science[4] identified four genetic variations in IFIH1 which independently lowered the risk of TID by more than 50%. A helicase enzyme, IFIH1, triggers the secretion of interferons in response to viral infections, which in turn up-regulate the MHC class I molecules in beta cells (post-viral infection) leading to T cell response and beta cell death. Disabling the expression of IFIH1 lowers the risk for TID. This is important in the context of earlier findings that suggest that entero-viruses (implicated in the etiology of TID), which replicate faster are associated with TID and those which replicate slower are not.

These studies in the etiology of the disease and other NIH funded studies on newborn screening and follow-up (TEDDY consortium or the The Environmental Determinants of Diabetes in the Young) identify the need for prevention. This study identifies environmental factors pre-disposing to or protective against islet auto-immunity and TID[5] Between 2004-2009 TEDDY has been screening...
Alum Formulated GAD is the only antigen-based vaccine candidate which has been shown to be effective in both T1D and Latent Autoimmune Diabetes in Adults or LADA. In LADA, five year follow-up results have now been published in Diabetologia, (2009) which showed excellent beta cell preservation. In vaccine doses of 20 µg and 100 µg, vaccinated patients only 14% required insulin at five years compared to 70 to 80% needed insulin in placebo, 4 µg and 500 µg doses.

Several ongoing studies (listed below) will make the vaccine useful in established T1D patients: (a) Large-scale phase III clinical trials are being conducted in Europe and the United States to confirm these findings. When completed and if approved, the vaccine is likely to reach the market in 2011, (b) Approval has also been obtained from the Swedish Drug controller authorities for using the vaccine in prevention of TID in children at risk for developing the disease. (c) Norwegian Drug controller Agency has given approval for the GAD vaccine to investigate the disease process before TID onset and if treatment with GAD vaccine stops the process. A unique feature of this study is that tissue samples from pancreas are allowed to be taken. Analysis of these tissue samples can provide direct insight into how GAD vaccine works to reduce beta cell destruction. This study will include 90 adults at high risk for developing T1D and additional 60 recent onset T1D patients. (d) Most interesting aspect of the new study (approved by FDA) is to treat established TID in children with vaccine for beta cell regeneration either alone or in combination with beta cell regenerative agents like: Lansprazole and sitagliptin.

This study is funded and carried out by NIH in Bethesda, USA. If shown to be successful, this will allow GAD vaccine to be given to all recent and old-onset TID for beta cell regeneration. This vaccine is produced by the Swedish company, Diamyd.

**DNA- based Antigen specific Immunotherapy using Proinsulin**

The candidate proinsulin vaccine is called BHT-3021 which is a DNA based antigen specific immunotherapy currently in Phase I/II clinical trial in patients with T1D. BHT-3021 is a plasmid encoding proinsulin, designed to target specific pathogenic immune cells responsible for the autoimmune response in type 1 diabetic patients. The compound has shown efficacy in NOD mice, a model of type 1 diabetes. In the current phase I/II trial, patients receiving BHT-3021 demonstrated preservation of C-peptide and an acceptable safety profile. BHT-3021 is designed to induce antigen specific tolerance by selectively turning off the errant autoimmune response attacking the pancreas. This highly specific immuno-modulation action could result in the preservation of pancreatic function and improved long term health in type 1 diabetic patients.

BHT-3021 was the subject of a recent presentation by Dr. Peter Gottlieb of the Barbara Davis Center at the
Antibody-based immunotherapy for T1D

CD3 monoclonal antibody therapy

Modified anti-human CD3 monoclonal antibodies was thought to be the next alternative to previously used OKT3 antibody for the prevention of T1D in NOD mouse. Mouse monoclonal antibody caused serious AE which were infusion related. Fc-mutated (Fc-nonbinding) monoclonal human CD3 antibodies were engineered and these were found to be less mitogenic, but were equally tolerogenic compared to functional Fc CD3 antibodies.[7,8] Two humanized CD3 antibodies are in different stages of clinical trials. They are the ChAglyCD3 antibody developed by Tolerx, USA (www.tolerx.com), with a single mutation (Asn→Ala) at residue 297 in the Fc region that prevents glycosylation, derived from rat YTH 12.5 antibody[8] and the hOKT3Ala-Ala antibody developed by Macrogenics, USA (www.macrogenics.com), with two mutations at residues 234 (Lue→Ala) and 235 (Lue→Ala) in the Fc region.[10]

CD20 monoclonal antibody therapy

Until recently B cells were thought to play an important role in priming T cells.[10] However, a recent study showed for the first time that B cells promote the survival of CD8+ T cells in the islets and thereby promote the disease.[12] CD20 is a cell surface marker expressed on all mature B cells. Rituximab (Roche/Genentech), a humanized anti CD20 monoclonal antibody (CD20 mAb) has been shown to successfully deplete human B cells from peripheral circulation via mechanisms involving Fc and complement mediated cytotoxicity and probably via proapoptotic signals.[13,14] Given the important role of B cells in maintaining the T1D, depleting B cells is a very interesting therapeutic option. TrailNet is currently testing the efficacy of rituximab (CD20 mAb) in a new-onset trial involving four week course treatment with the antibody.[15] This therapy has been developed by Genentech, now owned by Roche.

There is real hope for T1D patients both in early diagnosis and prediction as well as beta cell preservation and beta cell regeneration.

References


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