EDITORIAL

Traveling down the Long Road to Type 1 Diabetes Mellitus Prevention

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Type 1 diabetes mellitus, a chronic autoimmune disease that usually begins in childhood, affects more than 1.25 million Americans,[1] and its worldwide prevalence is increasing. Although insulin was discovered almost a century ago and the technologies for administering and monitoring insulin treatment have improved quality of life and reduced complications from the condition, the disease remains incurable. Accordingly, investigative efforts have centered on prevention, aiming to either delay or prevent disease onset. However, that requires the elucidation of the relevant pathophysiological mechanisms that lead to the pancreatic beta-cell destruction thought to be the root cause of type 1 diabetes. Early work focused on the identification of infectious or toxic causes of this destruction. Then, in an article published 40 years ago in the *Journal*, Eisenbarth and colleagues suggested an alternative idea — that there was a functional interaction of HLAs with autoantibodies to insulin in patients with polyglandular autoimmune failure and type 1 diabetes.[2] These observations seeded the field of endocrine immunology and led to revisions of theories about the pathogenesis of type 1 diabetes.

Currently, the pathogenesis of the condition is thought to be due to environmental triggers that initiate autoimmune destruction of pancreatic beta cells in persons who are at genetic risk, in whom endogenous antigens are expressed on target cells and presented by a complex with class I HLA. The highest-risk HLA genotype is DR3-DQ2, DR4-DQ8 (DQ8 represents DQA1*0301-DQB1*0302 and has been found to be associated with type 1 diabetes); by 12 years of age, a child who inherits the same DR3-DQ2, DR4-DQ8 genotype as a sibling with type 1 diabetes has a greater than 75% risk of the development of autoantibodies and a greater than 50% risk of the development of diabetes.[3]

As type 1 diabetes develops, lymphocytes, particularly CD8+ T cells, infiltrate and slowly kill beta cells.[4] The onset of the disease is gradual, and three clinical stages can be defined. Stage 1 is asymptomatic, characterized purely by the presence of autoantibodies; stage 2 is defined by an impaired metabolic response to a glucose load, although other metabolic indexes, such as the glycated hemoglobin level, remain normal; and stage 3 is marked by overt insulin deficiency, hyperglycemia, and loss of beta-cell function.

Herold et al. now report in the *Journal* the results of a phase 2, randomized, placebo-controlled, double-blind trial in which teplizumab, an Fc receptor–nonbinding antibody to CD3, was evaluated in relatives of patients with type 1 diabetes.[5] Teplizumab reduces the actions of CD8+ T lymphocytes on targets such as beta cells.[6] Previous, shorter trials of teplizumab in type 1 diabetes, all involving patients with early stage 3 disease, showed promise — although in one trial the results for the composite primary outcome (i.e., the use of insulin and glycated hemoglobin) were not significant.[7-9] In contrast, the present multinational trial was planned as a prevention trial involving high-risk persons (stage 2), with the primary outcome of time to diagnosis of overt type 1 diabetes. Eligible participants had two or more diabetes-related auto-

antibodies and evidence of dysglycemia on oral glucose-tolerance testing. Participants were assigned in a 1:1 ratio to receive a 14-day outpatient course of intravenous teplizumab or placebo; most were children (<18 years of age) and were followed for more than 3 years.

The results of this trial are striking, with several caveats. The annualized rates of new-onset type 1 diabetes were 14.9% per year in the teplizumab group and 35.9% per year in the placebo group. The median time to diagnosis of type 1 diabetes was 48.4 months in the teplizumab group and 24.4 months in the placebo group (hazard ratio, 0.41; 95% confidence interval, 0.22 to 0.78), after adjustment for age and antibody status. Not surprisingly, the greatest preventive benefit occurred in the first year of the trial, and the adverse-event profile showed a depression in total lymphocyte counts in the teplizumab group, although all these participants had a rebound in lymphocyte count during continued follow-up. In subgroup analyses, the presence of HLA-DR4 and the absence of HLA-DR3 were associated with more robust responses to teplizumab, as was the presence of anti–zinc transporter 8 antibodies.

Although the trial showed a marked delay in the onset of overt diabetes, the results should not be taken to imply that immune modulation constitutes a potential curative approach. Rather, these data provide strong albeit indirect evidence about the pathogenesis of beta-cell destruction and the potential to modify the course of type 1 diabetes with newer biologic agents. This trial will probably prompt the development of more refined screening criteria for treatment of persons at highest risk, although challenges in using immune modulators for type 1 diabetes remain.[10] This trial was small (76 participants) and involved only one 2-week treatment course. The duration and frequency of treatments, the long-term side effects of those therapies, the identification of subgroups of persons who do not have a response to the treatment, and the clinical course of persons who initially do have a response still need to be determined. Nevertheless, we can finally say, 40 years after Eisenbarth, that there has been substantial progress in modulating the early course of type 1 diabetes.

Disclosure forms provided by the authors are available with the full text of this editorial at NEJM.org.

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This editorial was published on June 9, 2019, at NEJM.org.

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DOI: 10.1056/NEJMe1907458