DIABETES

Teplizumab delays onset of type 1 diabetes mellitus

> This trial is the first to investigate a therapeutic aimed at delaying or preventing T1DM that met its end point

A phase II, randomized, placebo-controlled, double-blind trial has reported that teplizumab, an Fc receptor–nonbinding anti-CD3 monoclonal antibody, successfully delayed the onset of type 1 diabetes mellitus (T1DM) in a cohort of high-risk patients. Previous studies using this drug, which alters $CD8^+$ T lymphocytes (cells that are considered integral to β-cell destruction), have shown that treatment with teplizumab can reduce the loss of β-cell function in patients with T1DM for up to 7 years. The present study, however, is the first to show that teplizumab can successfully delay or prevent the onset of T1DM in people who do not yet have the disease.

The investigators of the present trial started by screening the relatives of patients with T1DM who did not have the disease to identify who were at high risk of future disease on the basis of autoantibodies and glucose-tolerance testing. "The screening process used in this study represents decades of work," explains corresponding author Kevan Herold from Yale University. This trial highlights the success of the work to identify patients who are at risk of developing T1DM, as three-quarters of patients in the placebo group went on to develop the disease.

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In total, 76 participants were selected for randomization. 52 days before enrolment, participants had to have had evidence of dysglycaemia (a fasting glucose level of 110–125 mg/dl), a 2-h postprandial plasma glucose level of >140 mg/dl and <200 mg/dl, or an intervening postprandial glucose level at 30, 60 or 90 minutes of >200 mg/dl on two occasions. All of the participants were >8 years of age and 55 were ≤18 years of age (median age in treatment group was 14 years (range 8.5–49.5) compared with 13 years (range 8.6–45.0) in the placebo group, and 57% of participants in the treatment group were male compared with 53% in the placebo group).

Participants were randomly assigned to receive either a 14-day course of teplizumab (44 participants) or placebo (32 participants). Participants in the teplizumab group were given a dose of 51 μg/m^2 of body-surface area on day 0, 103 μg/m^2 on day 1, 207 μg/m^2 on day 2, 413 μg/m^2 on day 3 and 826 μg/m^2 on day 4 through day 13. Progression to T1DM was assessed with the use of scheduled oral glucose-tolerance tests, the first of which were performed at 3 months and 6 months after the 14-day course of treatment or placebo, with the rest being performed at 6-month intervals.

This trial is the first to investigate a therapeutic aimed at delaying or preventing T1DM that met its end point, which was the elapsed time from randomization to the clinical diagnosis of T1DM (defined using criteria from the American Diabetes Association). In the teplizumab group, the median time to the diagnosis of T1DM was 48.4 months compared with 24.4 months in the placebo group. In total, 19 (43%) of the participants who received teplizumab and 23 (72%) of participants who received placebo were diagnosed with T1DM.

The authors found that a single course of teplizumab can delay or prevent progression to T1DM in high-risk, nondiabetic relatives of patients with T1DM. "I can't emphasize enough the benefit of not having T1DM for any amount of time," concludes Herold. "For example, consider a child who is currently between lower school and high school; delaying progression of the disease during this critical period of time in a child's life could have tremendous benefit to that individual."

The authors now intend to continue to follow up participants. As neither the regulatory authorities nor the general endocrine community have had to deal with the prospect of a practical, functioning preventive treatment before, Herold and colleagues are also beginning to address questions associated with this situation, with the view of moving forward to make this treatment available.

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ORIGINAL ARTICLE Herold, K. C. et al. An anti-CD3 antibody, teplizumab, in relatives at risk for type 1 diabetes. *N. Engl. J. Med.* https://doi.org/10.1056/NEJMoa1902226 (2019)