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T-cell targeted therapy tested in type 1 diabetes study

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Results from the START clinical study (Study of Thymoglobulin to Arrest Newly Diagnosed Type 1 Diabetes), led by Dr. Steve Gitelman (University of California, San Francisco) and sponsored by the Immune Tolerance Network (ITN), are published today in *The Lancet Diabetes & Endocrinology*. The study did not meet its primary endpoint: at 12 months, insulin production, as measured by C-peptide responses, showed no difference in overall decline between the treatment and placebo groups.

Thymoglobulin®, currently licensed for the treatment of organ transplant rejection, is a form of antithymocyte globulin (ATG), a mixture of specialized proteins called antibodies. These antibodies attach themselves to white blood cells known as T cells, interfering with their function and eliminating them temporarily from the bloodstream. During the development of type 1 diabetes, T cells mistakenly destroy the beta cells of the pancreas, which secrete insulin. ITN investigators hypothesized that treating new-onset type 1 diabetes with thymoglobulin would disrupt T-cell activation and might induce tolerance.

The Phase II START study enrolled 58 new-onset type 1 diabetic patients ages 12 to 35 years old. The patients were randomized 2:1 to receive ATG treatment or placebo. Patients in the ATG group received intravenous infusion of ATG over 4 consecutive days at the start of the study; patients in the placebo group received saline solution. At 6-month intervals, researchers measured insulin production of patients in both groups. The study was the first rigorous, placebo-controlled, multicenter

study of ATG therapy in patients with new-onset type 1 diabetes.

Further inspection of the ATG treatment group revealed two distinct rates of change during the 12-month period. Most of the decline in beta cell function occurred during the first 6 months. Interestingly, this initial rate of decline in function was limited to younger patients (ages 12 to 21 years old), whereas older patients (above 21 years of age) showed almost no reduction from baseline levels in insulin production over the 12 months. Almost all patients in the treatment group experienced serum sickness and cytokine release syndrome following ATG infusions, and the investigators suggest that this early cytokine induction may have led to the unfavorable loss of beta cell function, particularly in the younger patients.

Analyses of blood samples from START patients revealed that T cells rapidly decreased following ATG administration, consistent with the known mechanism of action of the drug. However, investigators observed notable differences between two specific T-cell subtypes during the first 6 months: the level of effector memory T cells, important mediators of inflammation, did not decline, while the level of regulatory T cells, which are beneficial in suppressing immune attack, were reduced.

Follow-up of subjects in this trial may yield additional insights into differences in response to ATG, and suggest biomarkers of safety and efficacy to be used in future new-onset type 1 diabetes trials. The high-quality clinical specimens collected throughout the study also will be an important resource for uncovering insights about the mechanisms of disease and identifying pathways to target in future studies.

Provided by Immune Tolerance Network