# Teplizumab: Is It a Milestone for Type 1 Diabetes or a Risk Factor for Other Autoimmune Diseases in the Long Term?

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In a recent issue of *Clinical Diabetes*, Jennifer D. Goldman and Hailey Choi reported that the U.S. Food and Drug Administration (FDA) has approved teplizumab, a new anti-CD3 monoclonal antibody therapy, for people who are ≥8 years of age and have stage 2 type 1 diabetes (i.e., have two or more diabetes-related autoantibodies and elevated blood glucose but no symptoms of diabetes) (1). This new therapy has been found to delay progression of the disease from stage 2 to stage 3 (i.e., the onset of symptomatic type 1 diabetes) (1). These findings seem promising, but how this new agent will reshape the progression of type 1 diabetes over the long term is unclear. Herein, we discuss a possible unexpected effect that could arise from teplizumab use based on the results of a comprehensive study we published with our colleagues in 2020 (2).

Our study included 159 patients between the ages of 11 and 18 years with type 1 diabetes, including 29 with diabetes plus Hashimoto thyroiditis and 26 with diabetes plus celiac disease. Additionally, one patient each had diabetes plus granuloma annulare, rheumatoid arthritis, hereditary progressive spastic paraparesis, Graves' disease, or vitiligo (2); because the number of these patients was statistically insufficent, they were not evaluated.

We evaluated the relationship between the duration of the partial clinical remission (PCR), or "honeymoon" phase, and the coexistence of other autoimmune diseases with type 1 diabetes. PCR of type 1 diabetes essentially depends on the amount of endogenous insulin production by residual pancreatic β-cells, and its length depends on the progressive destruction of these β-cells by the immune system (3). It is understood that teplizumab prolongs this period by throttling the immune system's T-cell attack on β-cells and maintains or improves insulin production (4). Our results showed that, as the duration of PCR increases, there are more cases of other type 1 T helper (Th1) cell–mediated autoimmune diseases associated with diabetes. In our study, patients who experienced >297 days of PCR seemed to be at greater risk of developing other autoimmune diseases associated with diabetes compared with those with <297 days of PCR (2). The prolonged production of insulin by the β-cells and consequent sustained continuous stimulation of the T-cell–mediated immune system causes a longer duration of PCR, which could predispose patients to developing other Th1-mediated diseases. The results of our study are important to consider when discussing the use of teplizumab, both because our study included a large number of participants and because our population was compatible with the target age-group for teplizumab.

In the TN10 (TrialNet Anti-CD3 Prevention) trial, 76 patients aged 8–49 years (with 72% <18 years of age) received teplizumab ($n$ = 44) or placebo ($n$ = 32) (5). Teplizumab therapy resulted in a statistically significant 25-month delay in the development of clinical type 1 diabetes. An update on the progress of the study was published in March 2021 showing that 50% of the teplizumab-treated group compared with only 22% of the placebo-treated group remained free of diabetes (6).

The PROTECT (Phase 3 Trial Evaluating Teplizumab in Patients With Recent-Onset Type 1 Diabetes) study (7) started in April 2019 to evaluate the effectiveness of teplizumab at the time of type 1 diabetes onset to prevent the loss of pancreatic islet cell function. Results are not yet available for this ongoing trial.

On 17 November 2022, the FDA approved teplizumab as the first disease-modifying therapy for type 1 diabetes. However, we think there are not yet sufficient data on the long-term effects of teplizumab, especially in the pediatric age-group. In the long run, we will be able to see whether it completely changes the way we approach

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preventing not only type 1 diabetes, but also other autoimmune diseases or, conversely, whether it poses risks for the emergence of other autoimmune diseases. For this reason, it is crucial to evaluate and discuss this issue now, early in the clinical use of teplizumab, to prevent unexpected negative outcomes in the future.

## DUALITY OF INTEREST

No potential conflicts of interest relevant to this article were reported.

## AUTHOR CONTRIBUTIONS

G.O. wrote the manuscript and researched the data. Both authors contributed to the discussion and reviewed and edited the manuscript. G.O. is the guarantor of this work and, as such, had full access to all the data reported and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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