Breakthrough drug helps children with new-onset type 1 diabetes: Phase 3 trial

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Children who were recently diagnosed with type 1 diabetes need less supplemental insulin to keep their blood sugar in a healthy range if they use the immunotherapy drug teplizumab, a new study reports.

Worldwide, about 8.4 million people have type 1 diabetes, an autoimmune disorder in which the immune system mistakenly attacks and destroys its own insulin-producing pancreatic beta cells, which regulate blood sugar levels. Teplizumab dampens down the destruction of the beta cells, helping to preserve the 10–40% most people still have at the time of diagnosis, but which are typically destroyed in the ensuing months. Maintaining these beta cells makes it much easier to manage type 1 diabetes.

"Type 1 diabetes is very difficult to manage and manage well, despite the emerging tools to aid patients, such as newer insulin analogs, insulin pumps and continuous glucose sensors," said Stephen Gitelman, MD, Mary B. Olney, MD/KAK Distinguished Professor in Pediatric Diabetes and Clinical Research at the UCSF Diabetes Center. "These challenges are especially apparent for children and adolescents dealing with type 1 diabetes."

Gitleman is the lead UC San Francisco researcher for the 61-site PROTECT study of teplizumab in the U.S., Europe and Canada. The findings, published in the *New England Journal of Medicine*, offer support for expanding treatment with teplizumab beyond its currently approved use for those who are at risk of developing type 1 diabetes but are not yet diagnosed.

"This is the first phase 3 trial of immunotherapy after diagnosis with type 1 diabetes that met its primary endpoint—i.e. was successful—and it showed a benefit for an extended period of time—18 months out," said Gitelman.

Phase 3 trials are meant to confirm findings from previous, smaller trials that a drug is safe and effective for its intended use. Immunotherapy aims to modify a person's immune response in order to restore a healthy balance or to maintain health.

"It's important to note that this study was done during the COVID-19 pandemic and patients didn't seem to be made more susceptible to the COVID virus, nor did they have any other problems fending off other infections," said Gitelman.

Clinical remission

In the PROTECT trial, children ages 8–17 years were randomized within six weeks of their type 1 diagnosis to receive teplizumab or placebo. The treatment, intravenous teplizumab, was given for 12 days at the start of the study and then six months later.

The participants were randomized 2:1 to receive either teplizumab or matching placebo. The teplizumab group of 217 patients preserved more of their remaining insulin-producing beta cells and trended toward needing lower doses of supplemental insulin to keep their glucose levels in a near-normal range, compared to the 111 children who received placebo.

Many more of the teplizumab-treated patients experienced a "clinical remission"—the ability to achieve tight blood sugar control using less supplemental insulin than those in the placebo group, Gitelman said. A full remission would mean not needing insulin at all.

Discovery of a lifetime

UCSF scientists and diabetes experts have been instrumental in discovering and validating teplizumab. Renowned immunologist Jeff Bluestone, Ph.D., the UCSF A.W. and Mary Margaret Clausen Distinguished Professor of Endocrinology and Metabolism emeritus and chief executive officer and president of Sonoma Biotherapeutics, played a critical role in developing teplizumab 37 years ago while working at

the University of Chicago.

After coming to UCSF, Bluestone continued his work to validate teplizumab, partnering with Gitelman and the UCSF type 1 diabetes clinical research team, along with Kevan Herold at Yale School of Medicine, to run key clinical trials on ways to delay, prevent and ultimately reverse type 1 diabetes. The current study is the culmination of a series of earlier, smaller studies in new onset type 1 diabetes that suggested teplizumab would be safe and effective in preserving beta cell function.

Their pivotal 2019 trial led to the FDA approval in late 2022 of teplizumab by showing that a 14-day dose of the drug delayed by an average of three years the onset of type 1 diabetes in children and adults who were at risk of developing the condition. Until then, the only approved treatment for U.S. patients with type 1 in the previous 100 years had been insulin injections.

Like a sledgehammer to the immune system

The current PROTECT study came after decades of work to determine how pancreatic beta cells could be preserved in people with new-onset type 1 diabetes.

"In earlier efforts, investigators conducted studies using broad, generalized immunosuppression to try to preserve the beta cells—the studies worked, but that is like putting a sledgehammer to the immune system, and could not be pursued due to general safety concerns with chronic immunosuppression," Gitelman said. "We then found more selective drugs that worked, but they never succeeded beyond phase 2 trials. This is the first phase 3 trial that has worked with immune-modulation."

Gitelman is already thinking about next steps. His team continues to follow the PROTECT patients to see how long the effects of the current therapy may last, and sees potential for studying whether these patients, or future ones, might benefit from additional teplizumab infusions at later time points. They are also considering whether the medication might be even more effective when used in combination with other drugs that work by complementary mechanisms.

Also, Gitelman noted, the incidence of type 1 diabetes is increasing in younger children, and a study is now being launched to evaluate the benefits of teplizumab when given to children under age 8 at risk for type 1 diabetes. Hopefully, these efforts in younger children will be expanded to new-onset type 1 diabetes studies as well, he said.

"Right now, my colleagues and I are excited and celebrating this moment," said Gitelman. "But we very much view this as the end of the beginning, and are actively planning for how to build on these findings and get even more robust results."

More information: Eleanor L. Ramos et al, Teplizumab and β-Cell Function in Newly Diagnosed Type 1 Diabetes, *New England Journal of Medicine* (2023). DOI: 10.1056/NEJMoa2308743

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