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Medical News & Perspectives

Type 1 Diabetes Advances Could Pave Way for Prevention

Jennifer Abbasi

For people living with type 1 diabetes, every day brings a series of calculations designed to strike a fine balance: inject just enough insulin to prevent sky-high blood glucose, without tipping the scales enough to cause dangerous hypoglycemia. Each time a patient hits on the just-right Goldilocks dose can feel like a minor victory.

Now, medicine could be one step closer to slowing down or possibly even preventing the disease. In a recent phase 2 trial, a 2-week intravenous course of an investigational drug called teplizumab delayed progression to type 1 diabetes compared with a placebo in people at high risk of the disease. The study was conducted by TrialNet, a federally funded research consortium that screens and monitors relatives of people with type 1 diabetes.

Audio

The study's 76 participants all had the condition in their family, which increases their risk about 15-fold. To join the trial, they also had to have at least 2 diabetes-related autoantibodies in their blood and abnormal results on a glucose tolerance test, indicators that they were on the cusp of the disease.

Researchers ended the study once 42 participants developed diabetes. At that point, 57% of those treated with teplizumab still didn't have the disease, while the same was true for only 28% of those who got the placebo. "It could be that the individuals in the teplizumab-treated group would develop diabetes the day after the study ended, or it could be that they will never develop diabetes," said Kevan Herold, MD, the study's lead author and a professor of immunobiology and internal medicine at Yale University in New Haven, Connecticut. "We're still very keen to find out what will happen."

Even if the drug doesn't provide lifelong protection, the study demonstrated a 2-year median delay in the diagnosis. Buying time before the chronic autoimmune condition sets in could make a big difference for the nearly 18 000 young people diagnosed with type 1 diabetes every year.

Herold recently spoke with *JAMA* about the study, recent advances in type 1 diabetes care, the cost of insulin, and what the future could hold for patients. The following is an edited version of the interview.

JAMA: Teplizumab is an anti-CD3 monoclonal antibody. How does it work?

DR HEROLD: CD3 is [a molecule] found on all T lymphocytes, immune cells that are involved in the pathogenesis of autoimmune diseases like type 1 diabetes. We have very good evidence that [teplizumab] delivers a signal to T cells and, as a consequence of that signal, the cells are rendered exhausted. In this case, our hypothesis is that by rendering the autoreactive T cells exhausted, we may be able to turn off the development of diabetes.

JAMA: In your study the median time to the diagnosis of type 1 diabetes was around 48 months in the teplizumab group compared with around 24 months in the placebo group. So the treatment delayed the disease. How significant is this finding?

DR HEROLD: It's a very statistically significant finding. But the more important question is what does this mean for people? I think everyone would agree that 2 years without diabetes is a gift. Type 1 diabetes is a disease that's with you literally 24/7. There is not a single activity that someone with type 1 diabetes does that in some way isn't affected by the disease, whether it's play if you're a child, whether it's eating, whether it's sleeping, whether it's going to school. So to not have the disease for 2 years is actually very important.

Most of the people in the trial were children. If you're a child about to go into middle school, and now all of a sudden you don't have diabetes until you're out of middle school, or if you're right about to go into high school and now you don't have diabetes until you go to college, and the same thing for college...that's huge. Delaying the time has important benefits in terms of emotional and social development.

JAMA: Do you suspect that there could be long-term health benefits to delaying type 1 diabetes for even a year or 2?

DR HEROLD: You have to follow the data and make sure. But the answer is yes, in general, I think so. I think that any time without diabetes is going to have some benefits. If you're an adolescent with type 1 diabetes, your hemoglobin A_{1C} [HbA_{1c}] is, on average, awful. [It] can be above 9%. So to not have diabetes during that period of time, I have a hard time believing it can't have some long-term benefits.

JAMA: Is there ongoing follow-up of the participants in this study?

DR HEROLD: Absolutely. Obviously we're interested in finding out if they will ever develop diabetes and, if they do, when. But we're also interested in knowing—even in those who did develop diabetes—is their diabetes improved? Is their ability to make insulin improved even though they may now have hyperglycemia and need to take insulin?

JAMA: Teplizumab is also being studied as a treatment for type 1 diabetes. But in 2011, the drug failed to meet the primary outcome in a phase 3 study of people with recently diagnosed disease, which was a composite of insulin use and HbA_{1C}. Are you still hopeful that the drug could help improve treatments for people who are already living with the disease?

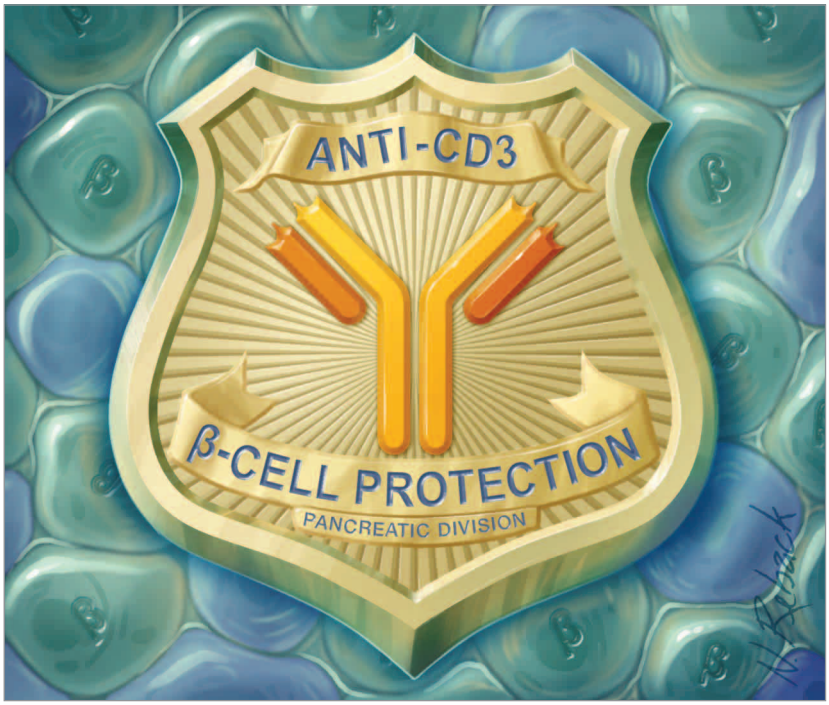
DR HEROLD: I'm very hopeful. That trial showed improvement in retention of β-cell function even though it didn't meet the composite end point. When most people present with type 1 diabetes, they still make clinically significant amounts of their own insulin. We know that β cells are always better at controlling diabetes than devices and exogenous insulin. The β cells are in the right place; they're in the pancreas. They release their insulin and it goes to the liver. They don't release too much. They turn it off when you don't need it. It's a perfect system in a sense. So to preserve the ability of your own β cells to make insulin is an important end point.

JAMA: Is the drug still being studied for treatment?

DR HEROLD: A phase 3 trial called PROTECT has just opened. That will be for patients with new-onset type 1 diabetes. Treating patients very early after the diagnosis is important. One of my colleagues in Europe has referred to type 1 diabetes as an immunologic emergency: you need to come in and treat patients at the very first signs that they're developing it. This new trial is enrolling people within 6 weeks of diagnosis. Most trials have enrolled people a little bit later.

JAMA: Are there any other treatments in the works that you're excited about?

DR HEROLD: There are a number of drugs that have shown the ability to preserve β-cell function in patients with new-onset diabetes. There has recently been some data published about the efficacy of



antithymocyte globulin, or ATG. Another drug called alefacept reduced severe hypoglycemia, which is the most frequent and most feared complication of the disease. And previous work suggested that a drug that targets B lymphocytes called rituximab had some efficacy. One of the interests now is to combine it with another drug, CTLA4-Ig, or abatacept, that may have complementary mechanisms of action.

I think it's fair to say that we ultimately will need some sort of a combination of drugs. Chronic immune suppression is a nonstarter, but that doesn't mean that a combination of agents—perhaps one that has a metabolic effect together with an immune modulator—might have significant improvement on clinical parameters in type 1 diabetes.

JAMA: Could any of these drugs be used in people who have been living with the disease for some time?

DR HEROLD: I have a feeling that's very complicated. It may be that there is a window of treatment opportunity just after disease onset. Having said that, there is a lot of interest in individuals who have long-standing diabetes who still may have residual β cells. When I was in medical school, we were taught that individuals who have type 1 diabetes kill all of their β cells. However, with more sensitive assays and larger studies, it appears that there are many individuals, even with long-standing diabetes, who still have some residual β-cell function. It's a bit of a dream at this point, but I think there is a lot of progress being made in understanding the biology of β-cell changes in response to the autoimmunity. The other option, of course, is to replace [β cells]. That potentially could be done with stem cells.

JAMA: The cost of insulin has skyrocketed. There are reports of people skipping doses and dying or traveling to Canada to get it at lower cost.

DR HEROLD: As someone who has been working in the field for a long time, the costs to me are absolutely unacceptable. Having lived in Europe for a period of time, where insulin was completely covered and the cost was considerably less, I just think it's wrong. This is a drug that's needed for survival. I don't think that we should be gouging individuals who have the disease.

These are drugs for the most part that have been around for many, many years. It would be one thing if there was an extraordinary research program to try to replace insulin or develop new insulins but, to be honest, I haven't seen it. I think that we are looking at a number of individuals who are taking advantage of the system in order to make profits,

quite frankly. And it's unfair for people who have diabetes.

JAMA: What does that look like for your patients?

DR HEROLD: At a minimum, insurers end up deciding what insulin a person can take. And there's a whole lot of restrictions on how you prescribe insulin. Somehow or another, my patients must get insulin. So we figure out ways to make sure they get it. But I've had patients who, because of costs, have skipped on insulin dosing. It truly is something that has to be fixed.

I was somewhat discouraged by the American Diabetes Association [ADA] statement about using the older insulins as a way to reduce costs [for patients with type 1 diabetes]. The newer insulins, the analogues, have much faster on and off time. When the β cells in the pancreas make insulin it works immediately and it's gone very quickly, too. The closer we can get to actually mimicking those kinetics, I think the more precisely we can be in control.

JAMA: Have continuous glucose monitors and the artificial pancreas, which combines continuous monitoring with an insulin pump, brought meaningful improvements?

DR HEROLD: I am a very strong advocate of the newer technologies. They're improving the lifestyle, and I think that the control is better and safer. It's a little unclear though whether this is going to broadly affect the management of diabetes. There are newer data suggesting that even with the newest technologies, you still don't achieve the goals of therapy that have been suggested by the ADA. So there seems to be improvement as you look at people one-on-one, but whether it's going to result in general improvement of diabetes care I think we still need to follow people and find that out.

JAMA: Type 1 diabetes is on the rise here in the United States and around the world. Do you have suspicions as to why?

DR HEROLD: [Into the 1980s] the incidence was about 12 or so per 100 000. [By 2012 it was] up to 21.7 per 100 000. It's becoming fairly clear that environmental factors can affect the progression to type 1 diabetes. There's been speculation that cleaning the environment, the more frequent use of antibiotics, and so on, may result in failures to develop immunologic tolerance that may ultimately lead to type 1 diabetes and other immune-related diseases.

JAMA: How far are we from a cure for type 1 diabetes and what could that look like?

DR HEROLD: It depends on what you call a cure, but I think some success in delay or prevention of diabetes opens up a whole new area of consideration. Some of these are going to be important social considerations. For example, now that we have something that could alter the progression to diabetes, should we be screening on a much broader basis? One potential way to a cure is to prevent it from happening. And I'm very excited about that.

In terms of what could be done for people who already have the disease, a lot of the cellular replacement technologies are starting to become very exciting. That potentially is another pathway to a cure. A cure also could mean that if you present with diabetes, you might be given immune therapy [like teplizumab], which would stabilize things. And then you might periodically come in, perhaps with a different agent or even the same agent, to maintain β-cell function. If you could maintain what has been called "the honeymoon" forever, that would be quite an accomplishment and coming close to a real cure. ■

Note: Source references are available through embedded hyperlinks in the article text online.

Debate Sparks Over LATE, a Recently Recognized Dementia

Jennifer Abbasi

This spring, a group of 35 experts introduced what they say is a recently recognized form of dementia: limbic-predominant age-related TDP-43 encephalopathy, or LATE. Aptly named, LATE strikes "the oldest old"—usually those in their 80s and 90s—causing progressive memory loss.

According to the group's report, which appeared in the journal *Brain*, the condition has largely flown under the radar in part because its symptoms mimic those of Alzheimer disease. The key difference shows up on autopsies. Some people with clinically diagnosed dementia have a buildup of misfolded TAR DNA-binding protein 43 (TDP-43) primarily in limbic brain regions, the areas involved in learning and memory, among other functions. These TDP-43 deposits are the hallmark that sets LATE apart from Alzheimer disease, according to Peter Nelson, MD, PhD, the report's lead author and a neuropathologist at the University of Kentucky in Lexington.

Nelson said that LATE helps to explain why many people with Alzheimer-type dementia don't have its characteristic cerebrospinal fluid or brain imaging biomarkers. Some of them could have LATE, according to his group. More frequently, however, TDP-43 inclusions coexist with β-amyloid plaques and tau tangles on autopsies, indicating that LATE and Alzheimer disease often go hand in hand.

The new classification is part of a larger evolution in how experts think about dementia. "It's becoming more and more clear that the initial thoughts that we had about the disease or diseases that underlie dementia were hopelessly inadequate in terms of encompassing the complexity and the heterogeneity of the actual conditions," Nelson said.

However, some say the field is moving too fast by defining late-onset dementia with TDP-43 as its own disease, before a true consensus exists.

A Strong Association

The report was the product of a 2-day workshop last October funded by the National Institute on Aging (NIA). International experts in brain imaging, clinical diagnosis, genetics, neuropathology, and neuropsychology met in Atlanta to name and define the disease and set research priorities.