THE FIRST-EVER TREATMENT TO DELAY TYPE 1 DIABETES IS LICENSED IN THE US

The US Food and Drug Administration (FDA) has approved Teplizumab, the world's first immunotherapy for type 1 diabetes to delay the condition in people at high risk, edging us towards a new era in type 1 management.

For the first time in history, there is a licensed treatment for type 1 diabetes that alters the course of the condition. Teplizumab, also known by its brand name Tzield, is now available in the US for people at high risk, after the FDA approved it as safe and effective at delaying the onset of type 1 diabetes.

Teplizumab is yet to be approved in the UK. However, it is currently under review with the UK Medicines and Healthcare products Regulatory Agency (MHRA). The FDA's decision paves the way for this life-changing treatment to be made available in the UK too.

Chris Askew, Chief Executive at Diabetes UK, explained why teplizumab's approval in the US is such a historic event. "It's the start of a seismic shift in how type 1 diabetes is treated," he said.

"For 100 years, people living with type 1 diabetes have relied on insulin to treat the condition, and the FDA's decision means that for the first time, the root cause of the condition – an immune system attack – can be tackled, and type 1 diabetes potentially delayed for up to three years."

Teplizumab is given as a daily infusion over 14 days. The monoclonal antibody binds to the T cells responsible for destroying beta cells to help neutralise their threat.

The FDA has specifically licensed teplizumab for use in adults and children aged eight years and older who currently have Stage 2 type 1 diabetes.

In TrialNet's staging of type 1 diabetes, Stage 1 is when people test positive for two or more islet autoantibodies – signalling that the immune system is earmarking beta cells for destruction.

In Stage 2, the destruction of beta cells has begun and an oral glucose tolerance test confirms that blood glucose levels are abnormal. However, people do not yet need insulin therapy and aren't experiencing any symptoms of high blood glucose. At this point, the lifetime risk of progression to clinical (Stage 3) type 1 diabetes is near 100%.

By Stage 3, more and more beta cells have gradually been destroyed. People can no longer produce sufficient insulin, leading to hyperglycaemia and the symptoms of type 1 diabetes.

Professor Colin Dayan who co-leads the type 1 diabetes Immunotherapy Consortium at Cardiff University said, "This very important announcement ushers in a new era for type 1 diabetes. For the first time in 100 years, new treatments can move away from focusing on improvements in insulin therapy and glucose control, to prolonging the period when insulin is not needed. And the possibility of making insulin treatment for type 1 diabetes in children a thing of the past, is in sight."

The long road to approval

Teplizumab has been a word on everyone's lips since 2019 when

first-of-a-kind findings were published in the New England Journal of Medicine[1] showing the drug could hold off the development of type 1 diabetes. In a clinical trial involving 76 people aged 8 to 49 years at Stage 2 of type 1 diabetes, 72% of people in the control group developed type 1 diabetes, compared to only 43% of the teplizumab group. Those that did develop type 1 diabetes during the study, were diagnosed a median of two years later, than people who had received the placebo.

The following year further results showed a continued beneficial effect, with the median delay now at three years[2]. New data also revealed that C-peptide levels not only stabilised, but increased in those treated with teplizumab, while in the placebo group levels kept declining. The improvement in C-peptide levels was associated with higher insulin secretion, lower blood glucose levels and researchers saw more exhausted T cells and fewer inflammatory cytokines in the teplizumab group.

The story of teplizumab, which started out as an anti-CD3 therapy, began in the 1980s. The idea was first hatched in the labs of Dr Kevan Herold and Dr Jeffrey Bluestone at the

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Dr Bluestone first theorised that an anti-CD3 therapy held promise for stopping the progression of type 1 diabetes in 1989, when working with cancer patients. The CD3 cell receptor recognises antigens that play a chief role in the activation of 'killer' T cells. By creating monoclonal antibodies and introducing them into the body, Dr Bluestone hoped they would occupy the receptor on T cells and prevent CD3 from binding. Early results from mice studies, published in 1992, seemed to back up this theory[3]. In the studies, 80% of mice began to produce significant levels of their own insulin again after treatment.

Over the following years, Drs Herold and Bluestone worked to establish effective doses of the anti-CD3 therapy and progressed onto small studies with people newly diagnosed with type 1 diabetes. Findings published in 2002, from a study of 24 people with new onset type 1, were another promising step forward, showing the treatment prolonged the period in which participants continued to make their own insulin[4]. Twelve months after treatment, two-thirds of those treated with the anti-CD3 therapy were producing the same or higher levels of insulin compared to the start of the study. Whereas in the placebo group, 10 out of the 12 people showed a steep reduction in their insulin production.

This culminated in a larger phase 3 trial involving 516 people with new-onset type 1 diabetes. Hopes were high that with this evidence the stage would be set for the drug's approval. But the results, revealed in 2012, were a major setback. No differences were found between the treatment and placebo groups for the primary endpoints of daily insulin doses and changes in HbA1c[5]. Plus, some significant side effects of flu-like symptoms emerged.

The researchers remained determined. After digging into the results further, they spotted that younger participants and those who'd started treatment sooner after their diagnosis seemed to respond better to treatment. And when looking at different outcomes, they saw that people treated with the therapy hung on to more of their own insulin-producing capacity than the placebo group.

Alongside these continued efforts, Drs Herold and Bluestone proposed a different sort of study. They would trial the therapy with people at high risk of type 1 diabetes who had not yet developed it. This bold move paid off and the results of that work led to November's approval.

Type 1 diabetes prevention in the UK

Here in the UK, the MHRA has awarded teplizumab an 'Innovation Passport' under the 'Innovative Licensing and Access Pathway'. This pathway is designed to help speed up access to promising new treatments in the UK. Teplizumab was one of the first drugs to be given this special status. It means the MHRA will accelerate its assessment of teplizumab and that key organisations, including the National Institute for Health and Care Excellence (NICE), are involved in the process from the start.

"The licensing of teplizumab in the UK must now be accelerated, and we're working with the NHS and with other diabetes charities and key stakeholders to ensure that people in the UK can benefit from this life-changing treatment as soon as possible," said Chris Askew.

If this happens, the immediate challenge then becomes finding people who are at high risk of developing type 1 diabetes in the future. A type 1 diabetes screening programme will be essential to reach those who could benefit from teplizumab, and other therapies in the pipeline, in the UK. You can read more about the launch of the ELSA screening trial and the steps being taken to help make sure the UK is ready on page 22.

Opening the floodgates

Much in the way that the first immunotherapy for cancer ushered in a new era of treatment a decade ago, teplizumab could open the door to further and bigger advances in immunotherapies for type 1 diabetes.

"At Diabetes UK, we are funding immunotherapy research to help people at all stages of type 1 diabetes. And we hope this monumental breakthrough will open the door for increased research investment, to develop further effective immunotherapies to treat the condition," explained Chris Askew.

Teplizumab's story is also far from over. The licensing for those aged eight years and older means it will come too late for many and there's work to be done to determine its safety and effectiveness for younger ages. Many are also asking if teplizumab could be given even earlier before Stage 2 and the destruction of beta cells has begun. Or if repeated treatments could help to extend the delay and continue pushing back the start of type 1 diabetes.

Excitement is also building around the ongoing PROTECT (PROvention T1D trial Evaluating C-peptide with Teplizub) phase 3 trial, expected to be completed in May. PROTECT is testing whether teplizumab preserves beta cell function in children recently diagnosed with type 1, building on the discovery from earlier trials that younger people appeared to benefit the most. PROTECT will include 300 participants between the ages of 8 – 17 years who will receive two 12-day courses of teplizumab six months apart. Positive results from PROTECT could lead to teplizumab getting approved for children with new onset type 1 diabetes.

Whatever comes next, the licensing of teplizumab has already rewritten the story of type 1 diabetes and is propelling us closer to the day when type 1 diabetes can be prevented or cured altogether.

References

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