The beginning of the end for insulin? – enter immunotherapy for T1DM

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Although we have treated type 1 diabetes (T1DM) with insulin for more than 100 years, it has been apparent since the discovery of insulitis in the 1960s and islet cell antibodies in 1974 that T1DM is fundamentally an autoimmune disease, not a metabolic disease.[1] Almost all other autoimmune diseases, from inflammatory bowel disease to rheumatoid arthritis, are treated with immunotherapy but not T1DM. In large part this is because of the discovery of insulin: unlike most other autoimmune diseases, a replacement therapy exists for T1DM. As a result, the discovery of insulin can be viewed as both a blessing and a curse. It is a "curse" because most of the major drug companies have developed their large immunotherapy portfolios of drugs for autoimmune diseases other than T1DM, including some such as psoriasis or alopecia areata that might be considered less life-threatening. And it is likely that diabetes practitioners are also partly to blame since they fear immunotherapy since it is a treatment with which they are not familiar.

It is important to remind ourselves of the challenges of insulin therapy. It is not a drug without risk: deaths still occur from underdosage (DKA) and overdosage (hypoglycaemia). According to ONS data, in 2021 in England and Wales, 44 people under the age of 50 died of DKA and 154 died of hypoglycaemia.[2] Set against this, even despite the introduction of CGM and insulin pumps, fewer than 30% of adults and children with diabetes achieve a target HbA_{1c} < 7.0%, or 53 mmol/mol which obviates the risks of long-term complications.[3] Furthermore, insulin management consumes millions of hours of patients and healthcare professional time in training, adjustments, testing and decision-making. Despite this, 36% of children and families continue to need psychological support more than five years after diagnosis (NPDA national audit 2018-2019,[3] and up to 50% of adults with T1DM report significant diabetes-related distress. [4]

There is a large and expanding world of highly selective immunotherapies that does not include the classic immunosuppressents (e.g. cyclosporin, tacrolimus) used in transplantation.

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Figure 1. Progression from multiple islet antibody positive to clinical T1D is almost inevitable.

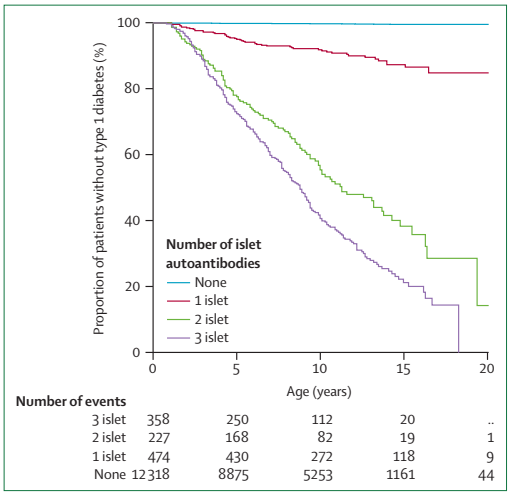

***Figure 1*: Proportion of patients without type 1 diabetes in relation to the number of islet autoantibodies after being followed up from birth**
Reproduced from Ziegler and colleagues,[6] by permission of the American Medical Association.

Ziegler AG *et al. JAMA* 2013;**309**(23):2473-9.

Rather, it includes many drugs known as "biologics" that have been widely used and have been very well tolerated in other autoimmune diseases for more than 20 years. Many are monoclonal antibodies, but small molecule inhibitors such as JAK kinase inhibitors are being introduced.[5] At least seven selective immunotherapies have shown efficacy in Phase 2 studies in preserving beta cell function from diagnosis compared to controls.[6,7] These treatments reduce progression of the underlying disease process but do not cause regrowth of beta cells. In current clinical practice, T1DM is diagnosed at the time that insulin replacement is required. This is late in the disease course, when it is estimated that more than 80% of functional beta cells have been lost. When selective immunotherapy is given at this stage, some impact on insulin dose (and in some studies also HbA_{1c} and hypoglycaemia rates) is seen, but it is too late to obviate the need for insulin.

Fortunately, it is possible to diagnose T1DM at an earlier stage. Multiple studies of birth cohorts in relatives of those with T1DM and the general population have shown that 80-90% of asymptomatic children who are found to have two or more islet autoantibodies (including anti-GAD, anti-IA-2, anti-ZNT8 or anti-insulin) will go on to develop T1DM (Figure 1). Once dysglycaemia develops (equivalent to impaired glucose tolerance), levels of hyperglycaemia

Figure 2. ADA classification of the stages type 1 diabetes

Table 2.1—Staging of type 1 diabetes (12,15)

	Stage 1	Stage 2	Stage 3
Characteristics	• Autoimmunity • Normoglycemia • Presymptomatic	• Autoimmunity • Dysglycemia • Presymptomatic	• Autoimmunity • Overt hyperglycemia • Symptomatic
Diagnostic criteria	• Multiple islet autoantibodies • No IGT or IFG	• Islet autoantibodies (usually multiple) • Dysglycemia: IFG and/or IGT • FPG 100–125 mg/dL (5.6–6.9 mmol/L) • 2-h PG 140–199 mg/dL (7.8–11.0 mmol/L) • A1C 5.7–6.4% (39–47 mmol/mol) or ≥10% increase in A1C	• Autoantibodies may become absent • Diabetes by standard criteria

FPG, fasting plasma glucose; IFG, impaired fasting glucose; IGT, impaired glucose tolerance; 2-h PG, 2-h plasma glucose.

ADA Standards of Care: *Diabetes Care* 2022;(Suppl1):S17-S38.

diagnostic of diabetes and requiring insulin will develop in more than 80% within five years.[8] This has led to the formal reclassification of T1DM into three stages by the American Diabetes Association, two of them preclinical (Figure 2).[9] Identification of individuals in early stage T1DM raises the possibility of intervening in the disease process before sufficient beta cell function is lost and insulin is required.[10]

Teplizumab

In 2019, Herold and colleagues from Diabetes TrialNet (www.trialnet.org) made the landmark discovery that immunointervention – in this case with the drug teplizumab that causes durable exhaustion of autoreactive T cells – at Stage 2 of Pre-T1DM could prevent the onset of stage 3 (clinical diabetes) by a median of 2-3 years.[11,12] Treatment with this "older" form of immunotherapy involves daily infusions over a 14-day course, but beyond this no further treatment is required and long-term safety seems excellent.[13] The advantages of a 2-3 year delay in the need for insulin are numerous: children (and adults) have 2-3 years during which they are at no risk for hypoglycaemia, have minimal requirement for healthcare, no requirement for treatment or regular blood monitoring and no dietary or lifestyle restrictions, while at the same time improving long-term outcomes by having an additional 2-3 years of near perfect glycaemic control. Importantly, beyond the first 14 days there is no burden of compliance required from the patient, so that even the least engaged people (such as teenagers and young people) can have the same outcomes.[7,14]

This remarkable finding led in 2021 to a historic "public vote" by an expert panel at an FDA scientific review, supporting the view that the benefits of immunotherapy in this form outweigh the risks (Figure 3). Most recently, on 17th November 2022, teplizumab was licensed for use in the USA (Figure 4). It was the first licensed immunotherapy for T1D,[15] contrasting with eight immunotherapies already licensed for psoriasis and similar numbers for inflammatory bowel disease, rheumatoid arthritis and multiple sclerosis.

Figure 3. The historic vote taken at the FDA advisory committee scientific meeting on teplizumab on 21st of May 2021, showing for the first time a vote 10:7 in favour of "the benefits of immunotherapy outweigh the risks".

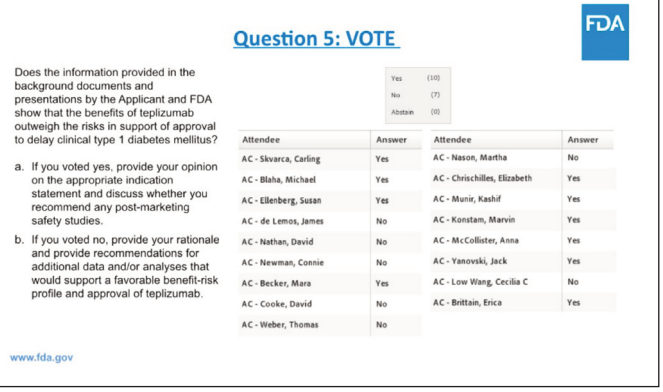

Figure 4. The FDA News release confirming marketing approval for teplizumab on November 17th 2022.[15]

FDA NEWS RELEASE

FDA Approves First Drug That Can Delay Onset of Type 1 Diabetes

For Immediate Release:

November 17, 2022

Today, the U.S. Food and Drug Administration approved Tzield (teplizumab-mzwv) injection to delay the onset of stage 3 type 1 diabetes in adults and pediatric patients 8 years and older who currently have stage 2 type 1 diabetes.

"Today's approval of a first-in-class therapy adds an important new treatment option for certain at-risk patients," said John Sharretts, M.D., director of the Division of Diabetes, Lipid Disorders, and Obesity in the FDA's Center for Drug Evaluation and Research. "The drug's potential to delay clinical diagnosis of type 1 diabetes may provide patients with months to years without the burdens of disease."

Not only does the advent of the first immunotherapy for T1DM provide the first major alternative to insulin since 1921, it necessitates a major change in the model of care. To give immunotherapy before insulin is needed and prevent its being required necessitates screening with autoantibodies to find individuals at stage 2, who are currently asymptomatic and not under medical care. One in 30 first-degree relatives of individuals with T1DM will be in stage 1/2 diabetes, of whom around 10% will be in stage 2.[16] Screening of relatives of patients with T1DM seems a reasonable start as these individuals are identifiable relatively easily identifiable, but this will only identify around 10% of cases since 85-90% of new cases of T1DM come from families with no history of T1DM. A national screening programme will ultimately be required to identify all cases prior to clinical diagnosis (stage 3).[17-19] The use of genetic risk scoring across 40-70 key loci in T1DM to identify those at greatest risk is now well advanced in T1DM.[20] Although it is a major undertaking, screening itself has benefits. Knowing that you or your child are in early stage T1DM markedly reduces late presentations in DKA and can prevent almost all hospital admissions at diagnosis,[21-25] allowing insulin therapy to be introduced in a structured way in the outpatient clinic. Currently, more than 25% of children present in DKA and more than 70% are ill enough to require hospital admission at diagnosis, an experience which many parents find very traumatic and one that can affect engagement with diabetes care for years to come.

Teplizumab is just the beginning. Once patients are identified in early stage T1DM, additional therapies can be introduced alongside or, if the disease appears to be progressing, to delay the need for insuin. Care needs to be taken to avoid excessive immunosuppression in combination therapy, but drugs such as the anti-TNF golimumab, shown recently to preserve beta cell function, are very well tolerated and require only a single subcutaneous injection every two weeks.[26] Oral therapies such as tyrosine kinase and JAK kinase inhibitors, which are already licensed for other autoimmune diseases including alopecia areata, are showing promise.[27] An intriguing recent discovery is that the well known calcium antagonist, verapamil also preserves beta cell function in new onset T1DM by reducing beta cell stress rather than impacting on the immune system.[28,29] This makes it a very attractive candidate for low-risk combination therapy.

The journey has started. Many challenges remain. In addition to national screening, the best way of monitoring disease progression in early phase T1DM is not known and no drug has yet been shown to be effective in the earliest stage (stage 1). Services will have to be reconfigured and all who work in diabetes retrained. Cost-effectiveness will need to considered. Most importantly, the major pharmaceutical companies will need to be engaged as in recent years the application of their increasing large immunotherapy portfolios of drugs has been directed away from T1DM to other indications.

But the prize is in sight. If we can extend the period of not requiring insulin to 6-8 years, the median age of diagnosis will be 18-20, and childhood-onset diabetes will gradually become a disease of the past. Continued beta cell preservation after diagnosis will also make insulin therapy easier and allow many more people living with diabetes to achieve glycaemic targets and avoid hypoglycaemia. Both of these in turn will delay the onset and severity of long-term complications. In the same way that rheumatoid arthritis has been transformed to being a disease of prevention rather than of joint replacement by immunotherapy, insulin will be relegated to "rescue therapy" and more and more patients will live longer, less burdensome and less troubled lives.

Key messages

- Type 1 diabetes can be detected at the preclinical stage by islet autoantibody testing
- Immunotherapy given at the preclinical stage can delay the need for insulin in type 1 diabetes.
- Multiple safe and well tolerated immunotherapies have shown promise in type 1 diabetes and the first has been licensed

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