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COMMENTARY

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What does the licensing of teplizumab mean for diabetes care?

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1 | INSULIN TREATMENT AND TYPE 1 DIABETES: TIME FOR SOMETHING DIFFERENT

In 1921, the discovery of insulin by Banting and Best presented a new era for people with type 1 diabetes (T1D), transitioning from calorific restriction and early death to enabling longer lives with insulin dependency. One hundred years later, the United States Food and Drug Administration (FDA) licensed the first immunoprevention agent, teplizumab, to delay the onset of T1D.[1] This marks a new era for T1D, focusing on identification of those at risk and treatment to modify the early disease course. A cure for T1D remains elusive but the last decade has witnessed an expansion of immunoprevention trials in children and adults, including the repurposing of agents successfully used in other diseases to modulate the autoimmune process and preserve beta cells.[2] It is anticipated that long-term delay will most probably be identified with combination therapy tested through adaptive and platform trials.[3] This commentary will provide the background to the licensing of teplizumab and the implications.

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2 | BACKGROUND

T1D is a T-cell mediated autoimmune condition caused by destruction of the insulin-producing pancreatic beta cells, found in the islets of Langerhans.[4] At diagnosis, around 80%-95% of beta cell mass is lost[5] and the individual becomes insulin dependent for life. Approximately 96 000 children aged younger than 15 years are estimated to develop T1D annually around the world.[6] However, T1D can occur at any age, with more than 40% of newly diagnosed individuals aged older than 30 years.[7] Recent advances in glucose sensing and insulin delivery technology aim to reduce the metabolic burden but fail to address the underlying autoimmune processes.[2]

Glycaemic targets in T1D continue to improve secondary to advances in technology and coordination of multidisciplinary care teams.[8,9] However, many individuals with T1D still do not meet glycaemic targets.[9-12] This excess glycaemic load confers future risk of chronic diabetes-related complications.[10,13] Even in the minority who achieve optimal glycaemic control, there is a 2-fold increased lifetime risk of cardiovascular disease and death in people with T1D, particularly in those diagnosed at a young age (< 10 years).[11,13]

Finally, the demands of insulin therapy cannot be overstated. The titration of insulin can be time-consuming, leaving limited time in clinic to address other issues. There is also significant patient burden with glucose testing and insulin boluses required multiple times per day,

combined with accurate carbohydrate counting. Increased access to continuous or flash glucose monitoring has helped individuals make more informed treatment decisions, improving quality of life and glycaemic outcomes.[14,15] Hybrid closed loop systems offer more effective treatment approaches but cannot eliminate the risk of severe hypoglycaemia or diabetic ketoacidosis (DKA).[16] Even if improved glycaemic control is achieved with assistive technologies, many individuals will continue to be exposed to the excess cardiovascular risks outlined above and the continual daily burden of insulin delivery.[17]

3 | EARLY DIAGNOSIS OF T1D

Birth cohort studies of relatives of people with T1D have shown that the emergence of circulating islet-cell autoantibodies (IAb) is the first stage of T1D.[18] Although not known to be directly causal, these autoantibodies are the hallmark of an autoimmune process against the beta cells. More than 80% of individuals with two or more different IAb (anti-insulin antibodies [IAA], islet antigen 2 antibodies [IA-2A], glutamic acid decarboxylase 65 antibodies [GADA] or zinc transporter 8 antibodies [ZnT8A]) detected in childhood will progress to T1D within 15 years, with an almost lifetime certainty of progression to insulin requirement.[18] The presence of at least two IAb with normoglycaemia on oral glucose tolerance testing (OGTT) is defined as stage 1 (fasting glucose < 5.6 mmol/L, 2-hour glucose < 7.8 mmol/L and midpoint glucose [30-90 minutes] < 11.1 mmol/L). The development of dysglycaemia marks the onset of stage 2, although the individual remains asymptomatic (fasting glucose 5.6-6.9 mmol/L, 2-hour glucose 7.8-11.1 mmol/L and midpoint glucose ≥ 11.1 mmol/L). Stage 3 T1D is defined by the traditional glucose cut-offs for diabetes (fasting glucose ≥ 7 mmol/L and 2-hour glucose ≥ 11.1 mmol/L) and may be asymptomatic (stage 3a) or symptomatic (stage 3b) with the classical osmotic presenting features, with the latter usually requiring insulin therapy.[19] T1D detected prior to insulin requirement (stage 1, 2 and 3a) allows a window of opportunity for therapeutic interventions that could alter the disease course and delay the need for insulin treatment.[20]

4 | A NEW ERA

Several immunomodulatory agents have been trialled in individuals with recent onset T1D (stage 3), with at least seven showing some benefit in phase 2 studies.[21] One of these is teplizumab, an Fc receptor non-binding anti-CD3 monoclonal antibody that modifies CD8+ T lymphocytes. Teplizumab has been shown to preserve residual beta cells in individuals newly diagnosed with T1D (stage 3).[22-24] For example, the Protégé study was a randomized controlled trial (RCT) undertaken in 513 individuals aged 8-35 years within 12 weeks of diagnosis. The randomization was 2:1:1 block treatment with teplizumab infused as a 14-day full dose, 14-day low dose or 6-day full dose compared with placebo. The primary outcome was insulin usage less than 0.5 units/kg/day and HbA1c less than 6.5% (< 48 mmol/mol) at 1 year. At 12 months, the number of patients requiring less than 0.5 units/kg/day with an HbA1c of less than 6.5% (< 48 mmol/mol) did not differ between the 14-day full dose (19.8%), 14-day low dose (13.7%), 6-day low dose treatment groups (20.8%) or the placebo group (20.4%).[24] In the teplizumab treatment groups, 5% of patients were not taking insulin at 12 months, whereas all patients in the placebo group required insulin by 12 months. Adverse events were similar between the treatment and placebo groups and the most common side effect was rash. However, at the 2-year follow-up, the prespecified secondary endpoint was met with a 14-day full dose of teplizumab preserving C-peptide compared with placebo. Post hoc analyses revealed that higher C-peptide at diagnosis (> 0.2 nmol/L), those randomized sooner after diagnosis (≤ 6 weeks), with lower entry HbA1c (< 7.8% [< 58 mmol/mol]), insulin usage less than 0.4 units/kg/day and younger age (8-17 years) achieved more effective C-peptide preservation following teplizumab treatment.[23] A closely related non-depleting anti-CD3 monoclonal antibody, otelixizumab, has also shown efficacy in C-peptide preservation,[25] but resulted in Epstein-Barr virus (EBV) reactivation in the doses used, and, when trialled at 16-fold lower doses, was not effective.[26]

Based on these results and those of the Abate study,[22] teplizumab was taken forward for testing in individuals with stage 2 T1D. A phase 2 double-blind RCT was performed in 76 individuals with stage 2 T1D aged 8.5-49.5 years comparing a single 14-day course of teplizumab with placebo in a 1:1 randomization. All participants were relatives of family members with established T1D and were identified from the TrialNet Natural History study.[27] The primary endpoint was time from randomization to diagnosis with stage 3 T1D. The median time taken to diagnosis of stage 3 T1D was 48.4 months in the teplizumab group compared with 24.4 months in placebo. At the 60-month follow-up, 19% of individuals treated with teplizumab had progressed to stage 3 T1D compared with 72% in the placebo group. The hazard ratio (HR) was 0.41 (confidence interval: 0.22-0.78), with annualized rates of T1D of 14.9% compared with 35.9% in the teplizumab and placebo groups, respectively. Individuals who were HLA-DR3 negative, HLA-DR4 positive and Zn-T8 negative were less probable to progress to stage 3 T1D. The expected adverse events were rash and headache. Transient lymphopenia was observed in the teplizumab group plus expansion of the KLRG1 + TIGIT+CD8+ T cells, associated with T cell unresponsiveness ('exhaustion').[27] In extended follow-up (72 months), median time to diagnosis was 59.6 months with teplizumab compared with 27.1 months for placebo, with an HR of 0.457. In the teplizumab group, 50% progressed to stage 3 T1D compared with 78% in the placebo group. Treatment with teplizumab was associated with C-peptide preservation and less decline in insulin secretion.[28]

The common side effects from teplizumab include myalgia (2%), headache (11%) and fever, as well as a peeling rash (36%), abnormal liver function tests (5%) and transient lymphopenia (70%). These are features of mild cytokine release syndrome, consistent with the mode of action of the drug (see below), and resolve without sequelae at the end of the treatment course.[27]

The mechanism of action of teplizumab remains incompletely understood. huOKT3γ1ala-ala, now known as teplizumab, was developed from an original murine anti-CD3 antibody first described in 1979 and used in transplantation (OKT3). Amino acid residues in the Fc binding region were mutated to reduce cytokine release syndrome triggered by binding via the Fc to monocytes. The antibody was also 'humanized' in non-target binding regions to reduce the induction of antidrug antibodies.[29] Teplizumab binds to the epsilon subunit of the CD3 complex present on all T cells, a key complex to mediate activation of T cells after coming into contact with antigen. At high concentrations, teplizumab inhibits T cell activation because it prevents signalling through the CD3 complex. It was originally believed to act by T cell depletion. However, the reduction in overall T cell levels is only transient with recovery within 6 weeks, consistent with the lack of long-term effects on infection risk. Rather, it seems that teplizumab is acting as a partial agonist of certain T cell subsets. Initially, this appears to cause margination of many T cells out of the circulation into lymph nodes (with a drop in circulating numbers), and subsequently a reduction in central memory T cells and an apparent rebound increase in effector memory T cells. More detailed analysis shows a particular increase in the CD8 T cell subset, CD57-KLRG1 + PD-1+, also expressing the inhibitory receptor TIGIT and the transcription factor EOMES. Cells of this kind are associated with 'exhaustion' (ineffective phenotype) in chronic viral infections, and these changes were detectable for up to 24 months after treatment with teplizumab. Lesser effects are seen in the CD4 compartment, with a possible increase in a subset of regulatory CD4 cells and an anergic phenotype in others.[30,31] Hence, overall, teplizumab in the dose recommended appears to act predominantly to inactivate highly activated effector CD8 T cells, including those targeting the beta cells, by driving them into an 'exhausted' state. Regeneration of these cells is slow, resulting in long-lasting effects. It remains unclear whether there is also an effect to promote other T cells that increase 'regulation' in the T cell compartments.

Delaying the onset of T1D comes with clear benefits. These include reduced insulin burden and hospital visits, a reduced diabetes duration, which could translate to fewer long-term complications,[32] better glycaemic control over the first 5 years[33] and potentially longer,[32] as well as an extension of the period during which the individual could benefit from further immunointervention. Delaying the onset from childhood, and into adulthood, particularly avoiding insulin dependence during adolescence, would be beneficial given the associated high glycaemic legacy observed in adolescents diagnosed in early life.[34,35]

On 17 November 2022, the FDA licensed Tzield (teplizumab-mzwv) for adults and children aged 8 years and older. This represents a first-in class licence for an immunoprevention agent for T1D. The licence comes with precautions, including premedicating and monitoring for cytokine release syndrome, risk of transient lymphopenia, risk of serious infections and hypersensitivity reactions, a need for age-appropriate vaccinations prior to commencement, and avoiding administration of live, inactivated and mRNA vaccines with concomitant use of Tzield.[1] Despite these stipulations, it is important to note that teplizumab does not result in long-term immunosuppression: circulating T cell levels return to normal within 6-8 weeks and the nadir is higher than that associated with conditions linked to immunodeficiency such as human immunodeficiency virus (HIV).[27] Thus far, safety data up to 7 years have shown no evidence of increased infection rates beyond the initial infusion period and no increased malignancy risk.[36] Teplizumab is an agent licensed for a defined, but as yet, largely unidentified population, because there are currently no universal general

TABLE 1 Anticipated benefits of screening and teplizumab therapy

Anticipated benefits of screening	Anticipated benefits of teplizumab therapy
1. Avoid acute illness and DKA at diagnosis[35] a. Educating family on the symptoms of T1D to improve recognition and help facilitate earlier diagnosis[33] b. Informing healthcare providers of at-risk status to increase index of suspicion if symptoms arise c. Offering monitoring follow-up to track progression d. Avoidance of hospital admission at diagnosis e. Reduce morbidity and mortality from DKA	1. Delayed onset of T1D a. Reduces burden from insulin treatment and hospital visits[2] b. Extending the early stage disease period to facilitate entry into further immunoprevention trials[2]
2. Identification of T1D at an earlier disease stage a. Facilitate a smoother transition to insulin therapy for the child and their family b. Reduce parental distress when diagnosed through screening compared with routine diagnosis[35]	2. Improved glycaemic control a. Offers a period of good glycaemic control of 2-3 y that requires minimal compliance at stage 2 disease[24] b. Preserves beta cell mass at stage 3 disease[22] c. Reduce the burden of high glycaemic legacy observed in early life.[2] Infers lower risk of long-term diabetes-related complications d. Improved glycaemic control for at least the first 5 y following insulin initiation (stage 3-4)[27]
3. Access to prevention trials a. Identify at-risk population who could benefit from prevention trials[2,20]	3. Treatment factors a. One-off 14-day infusion[24] b. Minimal side effects[25]

Note: An outline of the anticipated benefits of screening and the anticipated benefits of teplizumab therapy.
Abbreviations: DKA, diabetic ketoacidosis; T1D, type 1 diabetes.

TABLE 2 The application of Wilson and Jungner's guidelines for screening to T1D

Modified Wilson and Jungner classic screening criteria	Yes	No	Uncertain	Comments
1. The condition sought should be an important health problem	✓			
2. The target population for screening should be clearly defined and able to be reached			✓	Ages for testing need clarification
3. There should be an accepted treatment or course of action for patients who test positive that results in improved outcomes	✓			Teplizumab has been shown to delay stage 3 T1D by 3 years.
4. Facilities for diagnosis and treatment should be available		✓		Implementation in routine laboratories needed
5. There should be a recognizable latent or early symptomatic stage	✓			
6. There should be a suitable test or examination with appropriate performance characteristics			✓	Test performance needs validation at population level
7. The test should be acceptable to the population			✓	Will need testing in individual countries and communities
8. The screening test results should be clearly interpretable			✓	Double IAb positive defined Single IAb+ result not fully established
9. The natural history of the condition, including development from latent to declared disease, should be adequately understood	✓			
10. The cost of case-finding (including diagnosis and treatment of patients diagnosed) should be economically balanced in relation to possible expenditure on medical care as a whole	✓			Emerging evidence of cost effectiveness with prevention of DKA and long-term complications of T1D
11. The overall benefit of the programme should outweigh its harms			✓	More data needed on benefits and harm
12. Case-finding should be a continuing process and not a 'once and for all' project, with ongoing monitoring and development of the programme		✓		National screening programmes embedded in clinical care are required

Note: Application of the Wilson and Jungner criteria to screening for T1D. Guidelines are as described by Wilson and Jungner. Table adapted from Besser et al. (2022).[46]

Abbreviations: DKA, diabetic ketoacidosis; T1D, type 1 diabetes.

population screening programmes for early stage T1D outside of a research trial. An implementation strategy is needed, and the United States will be the first nation required to develop a pathway for identification, monitoring, treatment and ongoing management of those with early stage T1D.

5 | SCREENING TO IDENTIFY THE POPULATION AT-RISK

Screening for people at risk of T1D has largely relied on testing relatives of people with known T1D. Family members have a 15-fold increased risk of T1D compared with the general population.[37] Familial screening programmes such as Trialnet and INNODIA have performed autoantibody screening on 220 000 and 4400 first degree relatives, respectively, over the last 2-3 decades.[38] Screening programmes have shown a lower risk of DKA at onset of stage 3 disease, possibly because of improved awareness of T1D symptoms and metabolic surveillance to track progression.[39] However, because 80%-90% of individuals diagnosed with T1D do not have a family history of the condition, screening programmes that target first degree relatives will only benefit a minority of the T1D population.[40] For this reason, there are several general population autoantibody screening programmes emerging.[38] The Fr1da programme in Germany has screened more than 160 000 children aged 2-5 years. Children identified as presymptomatic T1D (stage 1 or 2) in Fr1da had a lower rate of DKA at onset of stage 3 disease (3.2%)[41] compared with Germany's national average for children diagnosed through usual care (20.8%).[42] The autoimmunity screening in kids (ASK) study in the United States suggested that the cost effectiveness of screening depended on at least a 20% reduction in DKA and a long-term improvement in HbA1c of 0.1% (1.1 mmol/mol) over the lifetime.[43] Ultimately, a general population autoantibody screening programme is required to identify the entire population eligible for treatment with teplizumab. The screening required to identify the population for teplizumab treatment is expected to bring the additional benefits of reducing the trauma of an unannounced diagnosis, hospitalization and acute illness (including DKA), improving the 'pathway to diagnosis', benefits that are separate from the action of the drug itself (Table 1). In the Fr1da study, although there was anxiety associated with receiving a positive islet

autoantibody test result, particularly in mothers, this was reduced to baseline at the 12-month follow-up and was lower compared with standard care, typically involving sudden onset diagnosis, and which may involve acute illness.[41]

Although the evidence base for general population autoantibody screening continues to grow, numerous questions remain. Sims et al. previously published a summary of international familial and general population screening programmes (Table 2 and Table S1 from Sims et al.).[38] In common, these general population screening programmes seek to assess feasibility, acceptability and cost effectiveness, and optimize autoantibody assays across different healthcare systems. Importantly, the optimal method for screening has yet to be determined, in terms of strategy (IAb alone or combined with genetic risk score), method of IAb sampling (dried blood spot vs. capillary vs. venous whole blood) and timing of IAb testing (single or multiple time points).[19,44,45] Adoption of a national screening programme will require many of the original screening criteria proposed by Wilson and Jungner to be addressed, and the evidence is building (Table 2).[46]

6 | ONGOING FOLLOW-UP AND INTEGRATING IMMUNOTHERAPY INTO DIABETES CARE

Following identification of at-risk individuals, education and follow-up are necessary to track progression towards clinical onset of disease and to prevent DKA and hospital admission at the point of diagnosis.[47] Note that teplizumab is only indicated for stage 2 (autoimmunity with dysglycaemia), which is present in around 10% of individuals identified as multiple antibody positive by screening. The majority of screened individuals (~80%) will be in stage 1 and will not be eligible for treatment for several years. Several factors are associated with a more rapid rate of progression from stage 1 to stage 2 or 3 T1D. These include the presence of dysglycaemia, at least three IAb,[18,41] the presence of IA-2A IAb, age younger than 2 years at the time of seroconversion[48] and elevated body mass index.[19,44,49] Many of these are captured in risk progression scores, such as the Progression Likelihood Score,[50] the Diabetes Prevention Trial Type-1 Risk Score (DPTRS),[51] the DPTRS60 and the Index 60 score.[52,53] Alternatively, continuous glucose monitoring[54] or autoimmune trajectories[55] can assist with prediction of disease progression. These metrics require integration into monitoring programmes and implementation into clinical care. The optimal method for monitoring during follow-up also needs clarification: both before and after teplizumab therapy; including the utility of tools to assess metabolic status (e.g. HbA1c or OGTT), risk scores, and the frequency and location of follow-up.[38,46] Currently, monitoring is offered through research programmes such as INNODIA, with 6-monthly OGTT testing for those with multiple autoantibodies and 2-yearly autoantibody screening for those with a single positive autoantibody. However, a universal screening programme and follow-up pathway that is integrated into clinical care is now needed. Treatment with teplizumab is probably best placed in specialist diabetes care teams so that rapport is built with longer-term care providers in preparation for insulin therapy. For individuals who decline follow-up, primary care providers should be informed about risk status and equipped with a higher index of suspicion for T1D, if, and when, symptoms arise.

7 | WHAT NEXT FOR IMMUNOTHERAPY?

A 2-3–year delay in symptomatic T1D following treatment with teplizumab is meaningful, but the real significance of the teplizumab licence is that it opens the way for other immunotherapies to further delay the onset of T1D. In recent years, several immunotherapy trials have shown promise. The following agents have been shown to preserve C-peptide in those newly diagnosed with T1D (within 6-12 weeks of diagnosis, stage 3 disease): golimumab, rituximab, abatacept and low-dose anti-thymocyte globulin in children and adults.[2,19] Anti-Il-21 combined with liraglutide has shown preserved beta cell function in adults.[56] Other trials for secondary prevention of stage 3 disease are ongoing, including iscalimab, GAD, baricitinib, low dose IL-2 and ustekinumab.[21] These studies are providing an extensive 'tool box' of agents that can be tested at earlier diabetes stages to delay the need for insulin further. Of particular recent interest is the cardiovascular drug, verapamil, which has been shown in two studies to preserve beta cell function in new-onset T1D, apparently by a direct action on the beta cell to reduce damage from the autoimmune process.[57,58] Because of its non-immune mechanism of action, it should be possible to combine verapamil with other immunomodulatory agents to achieve extended benefit.

The complex autoimmune processes that result in T1D may benefit from combination therapies targeting different aspects of the immune system to preserve pancreatic beta cells. Adaptive trials offer an approach to test multiple agents without undermining validity or integrity,[3] an approach that is used in other multifactorial diseases, such as oncology. The future of early stage T1D management will probably incorporate a personalized medicine approach with combination therapies. Evaluating response biomarkers would help to inform further or alternative treatments.[19]

8 | CONCLUSION

One hundred years since the discovery of insulin, there is a licensed therapy that targets the underlying autoimmune process. Teplizumab is the first-in class agent to be licensed in the United States for immunoprevention of T1D and its implementation will require a shift in our current approach to management. Significant exploration of how screening, monitoring and therapy can be integrated into clinical T1D care is needed. However, teplizumab and the therapies that are probable to follow give us an opportunity to bring about meaningful change for our patients.

AUTHOR CONTRIBUTIONS

LQ, RS, DT, PN, REJB and CMD have made substantial contributions to conception and design, or acquisition of data, or analysis and interpretation of data; been involved in drafting the manuscript or revising

it critically for important intellectual content; given final approval of the version to be published. Each author should have participated sufficiently in the work to take public responsibility for appropriate portions of the content; and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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DATA AVAILABILITY STATEMENT

Data sharing not applicable to this article as no datasets were generated or analysed during the current study

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