COMMENTARY

A Golden Hour and Golden Opportunity for β-Cell Preservation

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For the last several decades, most clinical trials and attempts to slow or stop autoimmune-mediated destruction of β-cells during type 1 diabetes (T1D) have focused on administration of immunotherapy shortly after clinical diagnosis. This approach changed gradually with the development of a new staging paradigm for T1D (1), which facilitated a framework where new therapeutic agents may be tested in stage 3 T1D and successful interventions advanced for testing at earlier stages of disease. Based on this approach, in late 2022, the U.S. Food and Drug Administration (FDA) approved teplizumab (Tzield) as the first disease-modifying therapy for T1D, with the indication of delaying the onset of stage 3 T1D in adults and children identified as having two or more islet autoantibodies and dsyglycemia (stage 2 T1D) (2). The approval of Tzield has ushered in an exciting new era in the field and serves as a capstone to nearly three decades of T1D clinical trial interventions. At last count, Tzield has been administered to nearly 170 adults and children (3).

Despite this remarkable success, there are still nearly half a million individuals who are newly diagnosed with stage 3 T1D each year (4). All these individuals lack an approved treatment option other than insulin replacement. While teplizumab is the first agent to show efficacy in stage 3 T1D and then successfully move to stage 2 testing and regulatory approval, nine other interventions have demonstrated positive effects on C-peptide when administered in recent-onset stage 3 T1D (5). However, none of these agents have advanced to regulatory approval, raising the important question of how we now bridge decades of positive clinical trial results with translation into an approved treatment for individuals progressing to a clinical diagnosis of T1D.

Approval of new therapeutic agents by the FDA is based on the presence of a clinically meaningful benefit, which is defined as an improvement in the way an individual feels, functions, or survives (6–8). The addition of nearly 3 years of insulin independence after administration of teplizumab in stage 2 T1D clearly met this bar when assessed by the FDA. In contrast, clinical trials initiated at stage 3 onset rarely, if ever, produce insulin independence. Rather, direct clinical benefit in stage 3 diabetes has been defined classically as an improvement in glycemic control, which is associated with a reduction in complication status (9), an actual measured reduction in complication status, or a decrease in the frequency of hypoglycemia (5,10). A multitude of challenges exist when applying these standards to trials conducted during the early peridiagnostic period. First, studies performed at stage 3 onset typically do not follow participants long enough to capture effects on hypoglycemia or complications, which can take years to develop. Second, glycemic control in the acute peridiagnostic period can be influenced by a number of potential confounders, including differences in insulin management and access to diabetes technology as well as social, biological, and demographic factors.

In 2004, in a consensus article/review that set the tone for the next two decades of intervention trials, Palmer et al. (10) suggested that C-peptide levels measured after a standardized mixed meal could serve as a surrogate outcome for β-cell function. In this issue of *Diabetes*, Latres et al. (5) reassess the evidence for C-peptide as an outcome and draw on several recent studies to strengthen the argument in support of using C-peptide as an "appropriate surrogate outcome to assess efficacy of disease-modifying therapies" initiated at stage 3 onset. A critical question is whether this

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gradually increasing evidence of the importance of C-peptide as a clinical trial outcome is sufficient to take immunotherapy for C-peptide preservation into clinical care.

Both the Palmer et al. and Latres et al. articles highlight foundational data from the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC) study, showing that it is possible to correlate longitudinal C-peptide levels with glycemic control and the frequency of diabetes complications and hypoglycemia in established T1D (9,11–13). To bolster the argument that C-peptide can be extrapolated as a read-out of these end points, Latres et al. summarize recent real-world data from the Scottish Diabetes Research Network Type 1 Biorepository Study and outcomes from islet transplantation. In short, these analyses suggest that a little goes a long way, as even modest levels of residual C-peptide can have meaningful effects on endpoints of interest. The authors add to these compelling data by showing results from a recent meta-analysis of stage 3 trials performed as part of the JDRF-funded TOMI-T1D (Trial Outcome Markers Initiative in Type 1 Diabetes) project, which analyzed patient-level data from 21 randomized controlled trials (RCT) of disease-modifying interventions performed in >2,900 individuals. This analysis adds direct evidence that C-peptide preservation in clinical trials performed close to T1D diagnosis is proportionally associated with an improvement in HbA_{1c}. In aggregate, these data show that a 55% improvement in C-peptide preservation was associated with a 0.64% lower HbA_{1c}. However, direct evidence of improvement in glucose variability and hypoglycemia was inconsistently measured and not available across all trials, making meta-analysis almost impossible (14). Nonetheless, taken together, the evidence landscape relating to benefits of preserved β-cell function has clearly been strengthened, with increased direct evidence of improved glycemic control and strengthened indirect evidence of protection from hypoglycemia and reduced complications with C-peptide preservation. Additional studies summarizing natural history data show that it is possible to estimate an individual's predicted rate of C-peptide decline postdiagnosis (15), and other analyses, including the TOMI-T1D study, have added insight into factors that predict response to immunomodulatory therapy. Not surprisingly, chief among these factors is baseline C-peptide (14,16).

With decades of aggregated clinical trial data, the approval of the first disease-modifying therapy in T1D, and the field's growing experience with administering immunomodulatory therapies, we believe the time is right to consider stage 3 T1D onset as an immunologic and metabolic emergency that merits intervention, a so-called golden hour for β-cell preservation. Capitalizing on this opportunity would require a concerted effort between the FDA, clinical trialists, pharmaceutical companies, and families affected by T1D to plot a path forward from clinical trials with positive outcomes on C-peptide levels to regulatory approvals in stage 3 disease.

While such a move has the potential to couple decades of clinical trial results with clinical implementation, we must not ignore the need for continued innovation in T1D clinical trial design. Important lessons come from the type 2 diabetes (T2D) field, where the use of HbA_{1c} as a surrogate outcome received particular scrutiny after rosiglitazone was shown to benefit HbA_{1c} but have a negative impact on cardiovascular outcomes (17,18). This finding moved the T2D clinical trial field toward more direct measures of meaningful benefit. The revelation that T2D RCT outcomes needed to focus on complications and mortality initially felt like an almost impossible challenge but has changed T2D intervention for the better. There are now numerous therapies that have RCT-level evidence showing direct benefit on these meaningful end points (19). Trialists in the T1D immune intervention field can learn from these recent successes in T2D treatment while also designing future registration trials to capture effects on end points that reflect direct clinical benefit and increased quality of life.

In closing, the hallmark teplizumab clinical trial, which showed a proven extension of insulin independence for individuals in stage 2 T1D, has facilitated the translation of immunotherapy into clinical care for T1D. This is an accomplishment that needs to be celebrated; however, it is now also important to focus on improving clinical outcomes and quality of life for individuals at all stages of disease. The successful approval of a disease-modifying treatment coupled with solidified evidence that C-peptide can serve as an appropriate surrogate for therapeutic efficacy offers a golden opportunity to revisit past clinical trials with positive outcomes performed at stage 3 T1D. Such a move could serve as a springboard for continued regulatory approval at all stages of disease progression, thus offering hope for all affected by T1D.

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