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Pediatric Endocrine Society Statement on Considerations for Use of Teplizumab (Tzield™) in Clinical Practice

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Abstract
Teplizumab (Tzield™, Provention Bio), a monoclonal antibody directed at T-cell marker CD3, is the first medication approved by the FDA to delay progression from stage 2 to stage 3 type 1 diabetes. To date, the overwhelming majority of pediatric endocrinologists do not have experience using immunotherapeutics and seek guidance on the use of teplizumab in clinical practice. To address this need, the Pediatric Endocrine Society (PES) Diabetes Special Interest Group (Diabetes SIG) and Drug and Therapeutics Committee assembled a task force to review clinical trial data and solicit expert recommendations on the approach to teplizumab infusions. We present considerations on all aspects of teplizumab administration, utilizing evidence where possible and providing a spectrum of expert opinions on unknown aspects. We discuss patient selection and prescreening, highlighting the safety and considerations for monitoring and treatment of side effects. We propose a schedule of events, a protocol for administration, and discuss practice management aspects. We advocate for

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the need for further long-term systematic surveillance studies to continue evaluating the efficacy and safety of teplizumab.

Introduction

A novel, disease-modifying medication teplizumab (Tzield™, Provention Bio) was approved by the FDA on November 17th, 2022 for adults and pediatric individuals ≥8 years of age with stage 2 type 1 diabetes (T1D) to delay the onset of stage 3 T1D [1]. The FDA-approved label leaves many decisions open to prescriber interpretation. To date, most clinicians administering teplizumab have relied on the Type 1 Diabetes TrialNet research protocol (TN-10) which provided the data to obtain the FDA label for treatment of individuals at stage 2 T1D [2]. Several real-world challenges related to defining eligibility for treatment, surveillance for and mitigation of potentially serious adverse effects, and addressing logistics of the 14-day infusion protocol require guidance and development of consensus for clinical administration.

To address this need, the Pediatric Endocrine Society Diabetes Special Interest Group (SIG) and Drug and Therapeutics Committee assembled a task force to provide expert recommendations on the approach to teplizumab infusions in the real-world setting. This statement aims to consolidate the existing data, clinical experiences, and insights gained from clinical investigators and diabetes clinicians to advocate for optimal clinical practices, facilitate a risk-benefit assessment, and address existing barriers to treatment. Given a lack of sufficient evidence to answer some of the questions, we provide a spectrum of opinions in hopes to educate clinicians about further developments in the field. Bulleted and highlighted statements represent the areas thought to be of critical importance and where consensus was reached between the experts and members of the PES Diabetes SIG and Drug and Therapeutics Committee. We will provide additional information beyond the TN-10 published data and highlight safety and monitoring considerations. We also seek to highlight the need for further long-term systematic surveillance studies to continue evaluating the efficacy and safety of teplizumab.

Mechanism of Action, Efficacy, and Safety

Mechanism of Action

Teplizumab is a humanized, anti-CD3 monoclonal antibody affecting the autoimmune-mediated destruction of beta cells through several effects on subpopulations of T cells, including reduction of the effector function of T cells, increase in the number and function of regulatory T cells, and "exhaustion" in a subset of effector CD8+ T cells [3–7]. The mechanisms of action are still not fully elucidated but overall suggest that teplizumab is not immunosuppressive, but instead functions largely as an immune modulator rebalancing effector and regulatory T cells.

Efficacy and Safety Data from Clinical Trials

In the phase 2, placebo-controlled, double-masked, pivotal TN-10 study (n = 76, median age 13 years [range 8–49], 72% < 18 years of age, 97% white), a single 14-day course of teplizumab was found to delay the median time to progression from stage 2 to stage 3 T1D by 24 months [2]. Prolonged cohort analysis by Sims et al. [8] showed that 22/44 (50%) of the teplizumab treated and 25/32 (78%) of the placebo-treated participants progressed to stage 3 T1D through 923 days of follow-up (range of 74–3,119) (Cox model adjusting for stratification and age: HR = 0.457 p = 0.01). An integrated analysis of C-peptide data from 609 persons (375 teplizumab-treated and 234 control) across five clinical trials in stage 3 T1D confirmed β-cell preservation but was unable to address whether the benefits of a second course of teplizumab are greater than those of a single course [9–13]. The PROTECT trial, a phase 3 randomized placebo-controlled study of two 12-day courses of teplizumab administered to children and adolescents (n = 318) with new-onset stage 3 T1D within 6 weeks of diagnosis and again 26 weeks later, confirmed the earlier salutary effects of teplizumab in new-onset T1D, showing a significantly higher stimulated C-peptide level in the treatment group (n = 217) (least square mean difference between the groups from baseline to 78 weeks 0.13 pmol/mL, 95% CI: 0.09–0.17; p < 0.001), with favorable trends in a number of secondary clinical endpoints [14].

In addition to 44 persons randomized to teplizumab in TN-10, the FDA new drug application cited safety data from four stage 3 T1D clinical trials including 773 pediatric and adult persons in the integrated safety study who received 1 or 2 courses of teplizumab [2, 10–13]. Herold et al. [13] subsequently reported that most adverse events (AEs) were mild to moderate in nature, transient and self-limited, and occurred primarily during drug administration. The most common adverse events included lymphopenia, rash, headache, and mild to moderate cytokine release syndrome (CRS) [1, 13]. AEs led to permanent study drug discontinuation in 14.3% of patients in the treatment group versus 3.7% of individuals in the placebo group; abnormal

Table 1. Teplizumab eligibility checklist

• **Age ≥ 8yo** • **≥ 2 T1D relevant antibodies (Glutamic acid decarboxylase 65 (GAD-65), Insulinoma-associated antigen 2 (IA-2), islet-cell antibody (ICA), Insulin antibody (IAA), Anti-zinc transporter 8 (anti-ZnT8)** **GAD-65 - Yes/No, Date(s): _____, IA-2 - Yes/No, Date(s): _____, ICA - Yes/No, Date(s): _____, IAA - Yes/No, Date(s): _____, anti-ZnT8 - Yes/No, Date(s): _____.***
At least one of the following: • **OGTT with impaired dysglycemia, within the preceding 6 months **** **Fasting glucose: 100-125 mg/dl (5.6 to 6.9 mmol/L), OGTT 30, 60, 90 min postprandial glucose: over 200mg/dl (11.0 mmol/L), 2-hour postprandial glucose: 140 to 199 mg/dl (7.8 to 11.0 mmol/L)** **Fasting: _____mg/dl, 30min: _____mg/dl, 60min: _____mg/dl, 90min: _____mg/dl, 2h:_____mg/dl** • **Hemoglobin A1C 5.7 to 6.4% or 10% or greater increase in HbA1C even in the normal range**
• **All age-appropriate vaccinations were administered prior to starting teplizumab.** • **Screenings for active CMV, EBV, Hepatitis, HIV, and tuberculosis are negative.** • **Discussed potential risks & benefits, and potential adverse events with patient and family.**

*Teplizumab prescription information indicates ≥2 T1D antibodies. Some individuals can lose antibodies over time; therefore, there is no time expiration of a historical evidence of multiple antibodies. If not repeating antibodies, ensure testing is done at a CLIA/CAP certified reference laboratory with an assay that ideally has a high specificity and positive predictive value. **Consider repeating OGTT on a separate date if no other signs of dysglycemia. ***Consider Hemoglobin A1C change >10% even if under 5.7%.

biochemical parameters, mainly transaminitis and hematological abnormalities, were the most frequent reasons. A similar safety experience was noted in the PROTECT trial [14]. Safety data are discussed in more detail in the Monitoring and Mitigating Adverse Reactions section below.

Prescriber Information, Practical Considerations, and Unanswered Questions

Patient Selection, Dosing, and Administration

Patient Selection: the current teplizumab approval is limited to persons aged 8 years and older with stage 2 T1D [1]. The clinical history should not suggest type 2 diabetes. The FDA label follows American Diabetes Association (ADA) T1D staging criteria [15] defining stage 2 as having two or more positive islet autoantibodies and dysglycemia by an oral glucose tolerance test (OGTT) or an alternative method if an OGTT is not available (Table 1). It is worth noting that the pivotal TN-10 study had different enrollment criteria and HbA1C was not a qualifying factor. In addition, autoimmunity and dysglycemia had to be persistent and documented on two separate samples obtained within 6 months before randomization. Further amendment to the study in 2014 eliminated the requirement for the second abnormal OGTT in a small number of participants <18 years ($n = 8$) [2] because the rates of T1D progression to stage 3 were similar in individuals with or without a confirmatory OGTT in this age group. Thus, the teplizumab label which reflects ADA staging criteria [15] and is different from the inclusion criteria used in TN-10 study. The proposed approach for patient selection and teplizumab

Table 2. Event schedules for before, during and after infusions

Pretreatment: need to have all of these to proceed	• No active serious infection or chronic active infection other than localized skin infections • Vaccines up to date • Hemoglobin >10 g/dL • Platelets> 150,000 platelets/μL • Lymphocyte count >1,000 lymphocytes/μL • Absolute neutrophil count >1,500 neutrophils/μL • ALT or AST <2 times the upper limit of normal (ULN) and bilirubin <1.5 times ULN • No laboratory or clinical evidence of acute infection with EBV or CMV • Negative rapid testing for COVID-19 • Negative pregnancy test for females of reproductive age
On infusion days	• Review any laboratories (see Table 4 for when to hold or permanently discontinue the infusion) • MD/APP evaluation of any new or worsening symptoms • Premedicate with an antipyretic and diphenhydramine at minimum on days 1–5 and PRN symptoms • Ensure home supply of ibuprofen, acetaminophen, diphenhydramine, and ondansetron • Observe for any immediate reactions
After the treatment course	• Follow laboratory tests 1–4 weeks posttreatment depending on severity of abnormalities at end of infusion and then periodically until abnormalities resolved • Educate the individual and their family on signs and symptoms of stage 3 T1D • Consider instituting a surveillance protocol trending OGTT or CGM results at least every 6 months using threshold values diagnostic for stage 3 T1D

Table 3. Sample of schedule of events

Day	Prior to infusion	1	2	3	4	5	6	7	8	9	10	11	12	13	14
Physical exam[a]	X	X	X			X				X					X
Vital signs	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
CBC/differential	X	X		X		X			X						X
Basic metabolic panel	X														
AST/ALT/Bili	X	X		X		X			X						X
Infectious agents[b]	X														
Urine pregnancy[c]		X													
Rapid testing for COVID-19		X													
Premedication: antipyretics		X	X	X	X	X									
Diphenhydramine		X	X	X	X	X									
Intravenous fluids[d]															
Infusion dose, μg/m^2		65	125	250	500	1,030	1,030	1,030	1,030	1,030	1,030	1,030	1,030	1,030	1,030

This is a proposed clinical follow-up and laboratory testing frequency. We recommend more frequent monitoring for any abnormalities until their full resolution as clinically indicated. ANC, absolute neutrophil count; EBV, Epstein-Barr virus; CMV, cytomegalovirus; HIV, human immunodeficiency virus, TB, tuberculosis; CRS, cytokine release syndrome. [a]Physical exam should be completed any day that there is a change in clinical status or staff or patient concerns. [b]Serology and viral loads for EBV, CMV, hepatitis (B, C), and HIV, QuantiFERON gold for TB within 30 days of infusion and as clinically indicated. [c]If a female with reproductive potential. [d]Consider if dehydrated, or unable to drink due to intermittent nausea, or symptoms/signs of CRS as clinically indicated.

treatment consideration and schedule of events are summarized in Tables 1–3, respectively.

The staging of T1D reflects immunological progression and a decline in beta cell function. Both could be fluid between stage 1 and 2 particularly in teenagers with insulin resistance and stage 2 and early stage 3 T1D when a prominent honeymoon phase is achieved. Expert diabetes immunologists caution that without confirmatory antibody and OGTT testing, anticipated immunological diversity of teplizumab-treated individuals in real-world clinical practice will lead to a different expected efficacy compared to the efficacy reported in the TN-10 study. Therefore, some experts recommend a conservative approach of obtaining two separate blood tests for antibodies and two OGTTs, whereas others support confirmation of two or more autoantibodies while obtaining only a single abnormal OGTT. Finally, a third group supports the label indication without repeat antibody testing, as positive screening tests for multiple islet antibodies are rarely followed by negative confirmation tests [16]. Also, a precipitous progression from stage 2 to stage 3 T1D might logistically not allow sufficient time for confirmatory testing. Some clinicians point out the importance of considering the family history of T1D and multiple autoimmune conditions.

Based on task force committee discussions, some physicians are introducing an idea of using HbA1C and/or continuous glucose monitoring (CGM) trends in at-risk individuals to define dysglycemia. A recent study found that 10% or greater increase in HbA1C was comparable to OGTT in documenting the risk of progression to stage 3 T1D [17]. Of note, the median (IQR) A1C was 5.2 (4.9–5.4) % at baseline in TN-10 study [2] and CGM was not completed in TN-10 participants at enrollment. In the Autoimmunity Screening for Kids Study, time >10% spent in hyperglycemia >140 mg/dL (7.8 mmol/L) was found to have an 80% risk of progression to stage 3 T1D within 1 year in antibody-positive children [18]. Ylescupidez et al. [19] argued that CGM measures in individuals with multiple positive pancreatic antibodies are less predictive of T1D progression than OGTT-derived variables. Further research is needed to address the validity of these approaches. Three European diabetes research groups Fr1da, GPPAD, and INNODIA as well the JDRF sponsored international consensus guideline group have recently developed expert recommendations on monitoring progression of T1D diabetes at the preclinical stages that could serve as a framework for identifying candidates for teplizumab infusions [20, 21].

Vaccinations: to ensure appropriate immune responses and safety, it is not recommended to administer inactivated or messenger RNA vaccinations within 2 weeks before starting teplizumab treatment, during the treatment period, and for 6 weeks after completing the treatment. Similarly, live-attenuated vaccinations are not recommended within 8 weeks before initiating teplizumab treatment, during the treatment course, or up to 52 weeks after completing the treatment [1].

- We strongly recommend ensuring patients are up to date on all vaccines – including influenza and COVID-19 vaccines prior to administering teplizumab.

Acute and chronic bacterial and viral infections: the reports on EBV or CMV reactivation are rare, self-limited, and have not required antiviral therapy. Due to the immunomodulating nature of teplizumab, patients should be screened for active EBV and CMV infections prior to the start of therapy [1, 2, 13].

- We recommend testing serology and viral loads for EBV and CMV, hepatitis B/C, HIV serology, and TB testing (QuantiFERON Gold™) prior to starting teplizumab. In clinical experience, there have been significant variability and challenges in determining clinically significant results. We recommend consulting infectious disease specialists for borderline tests before making a treatment decision.

Pregnancy and lactation: o data are available on the use and effects of teplizumab during pregnancy or lactation; therefore, it is recommended to avoid the use of teplizumab during pregnancy and for more than 30 days (6 half-lives) prior to planned pregnancy to minimize exposure to a fetus. Pregnancy tests should be conducted before infusions, and reliable contraception methods should be discussed with males and females of childbearing age [1].

Intravenous access for infusions: teplizumab infusions can be administered via peripheral (peripheral IV, midline catheters) or central (peripherally inserted central catheter [PICC]) venous access. The selection of IV access is influenced by family preference, the presence of trained personnel, and local hospital policies. Some hospitals may not permit the maintenance of a peripheral IV outside the hospital facility, necessitating the need for a new peripheral IV daily or a PICC line.

Infusion schedule: it is expected to take a minimum of 2 h daily for the 14-day course, encompassing 30 min for premedication, 30 min for the infusion, and 1 h for post-infusion observation in the absence of adverse events. Additional time is necessary on the days of the pre-infusion blood tests. The times may vary depending on

Table 4. Selected AEs: frequencies from clinical trials and guidance to pause or discontinue teplizumab infusions (adapted from [1, 13])

Adverse events (AEs)	Teplizumab, $N = 791$ (%)	Control, $N = 245$ (%)	Hold	Permanently discontinue
Cytokine release syndrome (CRS)[a]	46 (5.8)	3 (1.2)	Severe CRS[b] 1–2 days	Severe CRS >2 days
Hematologic abnormalities				
Leukopenia	501 (63.3)	41 (16.7)	see below for specific lymphocyte and ANC criteria	See below for specific lymphocyte and ANC criteria
Lymphopenia	632 (79.9)	41 (16.7)	N/A	ALC <500 cells/μL and no recovery trend by day 7 (based on prescribing information. This was not a discontinuation criterion in the PROTECT study [13])[c]
Neutropenia	313 (39.6)	53 (21.6)	ANC <500 cells/μL (based on PROTECT study [13], no recommendation in the prescribing information)	ANC <500 cells/μL and no recovery trend by day 7[d]
Anemia	228 (28.8)	55 (22.4)	Hgb <10 g/dL	Hgb <8.5 g/dL
Thrombocytopenia	172 (21.7)	24 (9.8)	Platelets <50,000/μL (based on PROTECT study [13], no recommendation in the prescribing information)	Platelets <50,000/μL and no recovery by day 7[d]
Transaminase elevations				
AST increased	222 (28.1)	50 (20.4)	2 × ULN	5 × ULN
ALT increased	210 (26.5)	28 (11.4)	2 × ULN	5 × ULN
Biochemical abnormalities				
Hyperbilirubinemia			1.5 × ULN	3 × ULN
Blood bicarbonate decreased	303 (38.3)	67 (27.3)	N/A	N/A
Rash	273 (34.5)	25 (10.2)	N/A	N/A
Hypersensitivity reaction				Angioedema, serum sickness, bronchospasm
Acute/chronic infections				
New EBV infection	18 (2.3%)	10 (4.1%)	Hold, call for infectious disease consult, check serology or viral load for EBV, CMV, likely stop infusions	
EBV reactivation	40 (5.1%)	6 (2.4%)		
EBV viremia	25 (3.2%)	3 (1.2%)		
New CMV infection	5 (0.6%)	2 (0.8%)		
CMV reactivation	4 (0.5%)	N/A		
COVID-19	N/A	N/A	No infusions	
Other infections: hepatitis, HIV, TB			No infusions	

This guidance is based on the package insert and experience in clinical trials. Decisions regarding treatment interruption or termination require clinical discretion. Adverse events (AEs) reported at higher frequency in teplizumab versus control group were CRS, lymphopenia, leukopenia, rash, decreased blood bicarbonate. CRS, cytokine release syndrome; ULN, upper limit of normal; ALC, absolute lymphocyte count; ANC, absolute neutrophil count; CTCAE, common terminology criteria for AEs. [a]Fever, nausea, headache, myalgia, arthralgia, transaminase elevations (56% of AE, of which 64% were 2.5 times ULN, 32% were 2.5–5 times ULN, and 4.5% were 5–10 times ULN), and hyperbilirubinemia. Most cases were mild or moderate. Severe cases may occur. One clinical site had a patient experience severe CRS on the 7th day of the infusion (author's experience). [b]Severe CRS was considered as grade 3 to grade 5 of CTCAE criteria: grade 3: prolonged (not rapidly responsive to symptomatic medication and or brief interruption of infusion, recurrent of symptoms following initial impairment, hospitalization for other sequel like renal impairment or pulmonary infiltrates, grade 4: life threatening: pressor or ventilatory support, grade 5: death [1]. [c]This recommendation is based on prescribing information [1] only. Clinical trials have been conducted safely with a less conservative approach [14]. We suggest using clinical discretion in holding or discontinuing therapy for low lymphocyte counts. Lymphopenia is expected, recovery trend in ALC even if <500 could be reassuring. More data from clinical registry collecting treatment information is needed to address this recommendation. [d]In the PROTECT clinical trial [13], the decision on discontinuation of infusion for low ANC or platelet count was made by a study investigator in discussions with a study medical monitor.

the institutions' individual processes. Some practitioners prefer obtaining blood tests after an infusion to guide the management of the next day and save time. Although the time between daily infusions is not specified, maintaining a dosing interval close to every 24 h may theoretically decrease the risk of side effects.

- The infusion protocol should be carefully explained to the family to avoid interruptions.

Infusion settings: maintaining an uninterrupted 14-day schedule is challenging for many pediatric diabetes centers and can be burdensome for families. Potential solutions gleaned from personal communications involve utilizing an adult infusion center with a requirement for a pediatric nurse/APP/physician to be available at the bedside of a pediatric patient during and after the infusion. Other locations for infusions to consider include inpatient wards that allow outpatient beds. Hematology-oncology or sedation units are another option, as their staff are experienced in the treatment of cytokine release and hypersensitivity reactions and sensitive to mitigating the risk of infection. The necessity for a clinician to assess the potential adverse reactions during infusions may pose a staffing burden for some diabetes centers but can be billed with a modifier for adequate reimbursement.

- The efficacy of teplizumab in clinical trials was primarily determined from an uninterrupted continuous 14-day treatment course. The potential effects of dose interruption on teplizumab efficacy are currently unknown. We recommend avoiding interruptions in daily infusions, until more data become available. However, if a planned dose is missed, it is currently recommended to resume and complete the full 14-day course of treatment if the reason for discontinuation was not a contraindication to further treatment, such as a severe acute hypersensitivity reaction (see Table 4 for guidance on holding and permanently discontinuing the treatment for different AEs).
- While there has been consideration given to performing infusions with home healthcare/visiting nurse services or independent infusion centers, the standard of care in other disease states associated with potential severe acute side effects is to conduct infusions at infusion centers with adequate monitoring. A controlled clinical setting with nurses who are trained in Pediatric Advanced Life Support (PALS) or Advanced Cardiac Life Support (ACLS), depending on patient age, and with ready availability of an on-call healthcare physician/clinician for patient assessment if needed is highly recommended.
- In-home infusions in a pediatric population should be avoided for at least the first week or until the risk of significant AEs decreases, which varies among patients. Because the location of infusion must be decided prior to obtaining insurance approval, changing locations based on clinical needs may not be feasible. Ideally, home infusions should be limited to adult patients, and there must be a mechanism for prompt formal evaluation of the clinical status of the patient if an AE occurs, including after hours.

Dosing and administration: teplizumab is administered by IV infusion over 30 min once every day for 14 consecutive days. The recommended dosage regimen is 65 μg/m^2 on day 1, 125 μg/m^2 on day 2, 250 μg/m^2 on day 3, 500 μg/m^2 on day 4, and 1,030 μg/m^2 on days 5 through 14 (Table 3) [1]. Teplizumab is mixed by a pharmacist in a small bag (bags and tubing must be made of PVC). Teplizumab has limited stability and therefore the infusion should start within 2 h and completed within 4 h of preparation. If home infusions are considered, medication will likely need to be mixed at the bedside rather than sent from a central pharmacy. After completion of the infusion, normal saline is run through the line to ensure the complete delivery of the dose. Vital signs should be checked at baseline, every 15 min during infusion and at the end of the 1-h observation period post-infusion (Table 3).

Monitoring and Mitigating Adverse Reactions

Serious adverse reactions included CRS, lymphopenia, hypersensitivity reactions, and line infections. The frequency of AEs based on integrated safety study data [13] and recommendations on management of the adverse reactions are summarized in Table 4.

CRS is generally mild and well tolerated, developing in ~5% of persons [1, 13]. In an integrated safety study pool, 13% of CRS cases were considered as serious AEs [13]. Clinicians and infusion centers must be prepared to mitigate the effects, including emergency measures. CRS typically emerges during the first 5 days of teplizumab administration during the dose escalation phase, but can develop at any time during treatment, and signs and symptoms can extend up to 28 days following the last infusion [1, 2]. CRS encompasses a constellation of signs and symptoms and may include fever, nausea, headache, myalgia, arthralgia, increased alanine aminotransferase (ALT), aspartate aminotransferase (AST), and total bilirubin. Any of these possible signs and symptoms can be mild, moderate, or severe; for example, myalgia may be mild, but it can prompt a visit to an ED for severe pain. Signs and symptoms of CRS frequently start the evening after the first infusion and improve over a few days.

- To mitigate the CRS, the package insert recommends premedication with NSAID or acetaminophen, an antihistamine, and/or an antiemetic 30 min prior to the first 5 doses of teplizumab and may need to be continued longer. This premedication may be continued around the clock and for the whole duration of treatment if symptoms of CRS persist. Families should be instructed and prepared to administer those at home as needed.
- The authors suggest ibuprofen may be more effective and preferred than acetaminophen due to lower risk of liver enzyme elevation. In the setting of decreased appetite and consistent use of Ibuprofen, gastrointestinal prophylaxis with an antacid may be needed.
- Antiemetics (e.g., ondansetron) could be more useful not immediately before or after infusion, but later when an individual develops nausea in a home setting. While this does not necessarily need to be included in premedication, a supply should be provided to the patient to use at home as needed.
- In addition, we recommend ensuring adequate hydration to decrease the likelihood of adverse reactions. Generous oral hydration is often sufficient. IV fluids (e.g., 0.9 NS 20 mL/kg IV bolus) could be used for symptoms of CRS, nausea with poor oral intake, and as clinically indicated.
- Fever is a hallmark of CRS. Since premedications may blunt fever, it is important to monitor for other signs and symptoms and laboratory parameters of CRS.
- In the presence of fever, if other classic signs of CRS are not present, a broader differential diagnosis including a central line infection or a concomitant viral or bacterial illness must be considered and evaluated, perhaps with an inclusion of an infectious disease consult.
- A short course of glucocorticoids has been used and may be considered to mitigate signs and symptoms of severe adverse reactions and moderate to severe CRS. Potential effect of glucocorticoid on the efficacy of teplizumab is not known; therefore, expert immunologists overall discourage this approach unless clinically necessary.

Lymphopenia was observed in about 80% of persons who received teplizumab in clinical trials. It can be profound, typically reaching a nadir at days 4–5 of treatment and then recovering as treatment continues, normalizing by week six [1, 13]. Based on preclinical data, this likely represents transient migration of lymphocytes out of the bloodstream into tissues; the rapid recovery suggests that the lymphopenia does not result from T-cell depletion.

Anemia was observed in about 27% of persons who received teplizumab in pooled 5 clinical trials compared to 21% of placebo-treated individuals, recovering within 2–4 weeks of treatment. Almost 2% of subjects discontinued the treatment due to Hb <8.5 g/dL [1, 13].

Thrombocytopenia was observed in 13% of treated integrated safety study subjects; similar to anemia, it occurred during the 14 days of treatment and recovered within 2–4 weeks of treatment. In this population, 1% of patients discontinued teplizumab due to low platelets, 0.1% (1 patient) having a platelet count less than 50,000//μL [1, 13]. Neutropenia was seen in ~40% of teplizumab-treated persons versus 22% of placebo-treated persons in the integrated safety study [13].

- We recommend a baseline CBC with differential to ensure no underlying hematologic abnormalities and then monitoring it throughout treatment or until normalization of levels (see above and refer to parameters to hold and discontinue teplizumab, Table 4).
- We recommend considering recommending that persons receiving teplizumab wear masks during the seasonal increase in viral infections and that patients and immediate household contacts attempt to avoid all ill contacts as a precaution from 2 weeks prior to treatment until full recovery of lymphocyte and neutrophil counts.

Transaminase elevations were reported in 25% of the integrated safety study group with or without CRS and were mostly transient, resolving 1–2 weeks after treatment [1, 13]. Among persons who experienced CRS, transaminase elevations were observed in 56% (of which 64% had levels 2.5 times ULN, 32% had levels 2.5–5 times ULN, and 4.5% had levels 5–10 times ULN). Transaminase elevations leading to drug discontinuation occurred in 5.6% of the teplizumab group and 0.9% of the control group (communication with Provention Bio).

- The timing of expected lymphopenia and transaminase elevations support the expert recommendation to trend CBC, liver transaminases, and bilirubin during infusion course (Table 3). If there are laboratory abnormalities (e.g., elevated liver enzymes or significant drops in blood counts) or clinical concerns (symptoms of CRS), additional laboratory evaluations should be performed as clinically indicated. After the completion of infusions, we recommend rechecking relevant laboratory tests periodically until any abnormalities have resolved (refer to parameters to hold and discontinue teplizumab, Tables 2, 4).

Rash and hypersensitivity reactions, including anaphylaxis (0.1%), serum sickness (0.1%), angioedema

(0.3%), peripheral edema (1.6%), and urticaria (1.9%) occurred in the teplizumab group in the integrated safety study [1, 13].

- When severe hypersensitivity reactions occur, it is recommended to discontinue the use of teplizumab (Table 3). It is important to ensure the availability of epinephrine injection, oxygen, bronchodilators, dexamethasone or equivalent glucocorticoid, antihistamine medications, resuscitation equipment, and other supplies for the emergency management of allergic/toxic reactions; doses of all drugs are according to local, regional, or national recommendations. Trained personnel who can quickly recognize and respond are essential.
- Although the observed risk of hypersensitivity reactions appears to be low, monitoring in the post-market setting is important for further understanding of teplizumab's safety.

Rashes were observed in 48% of teplizumab-treated patients during the treatment, and most of them were nonserious, papular and pruritic, transient, and self-limited [1, 13].

- We recommend supportive care for pruritus, which may include the addition of another antihistamine or a low-dose topical steroid as a secondary treatment.

Infection rates were reported to be similar between teplizumab and control groups, but the rates of serious infections were higher in the treatment group (3.5 vs. 2% in control group) in the integrated safety study [13]. New EBV and CMV infections were also comparable between teplizumab and control group. Reactivation of EBV and CMV was observed more frequently in the treated group versus control group (5.1 vs. 2.4% for EBV and 0.5 vs. 0 for CMV) [13]. Many of the reactivations were in clinically asymptomatic individuals. And no one required antiviral therapy. The PROTECT study reinforced the notion that teplizumab therapy is immuno-modulatory, not immunosuppressive, as the trial was conducted through the middle of the COVID-19 pandemic and there was equal distribution of COVID-19 cases between teplizumab treated and placebo groups. None of the PROTECT participants required hospitalization or antiviral therapy [14].

There have been no malignancies reported to date that have been reported as attributable to teplizumab treatment, but more data and long-term follow-up are needed to further evaluate [13].

- If signs of infection occur during the treatment period, teplizumab should be paused and appropriate diagnostic testing completed based on symptoms. Consider checking serology and viral load for EBV and CMV. Infection should be resolved and/or an infectious disease specialist consulted prior to resuming treatment. It is important to note that CRS presents with fever, and clinical judgment is needed to distinguish fever from a possible infectious cause.
- Due to the risk of EBV and CMV reactivations and the associated theoretical risk of lymphoproliferative disease, long-latency risk should be addressed through the creation of an observational patient registry.

Hyperglycemia: based on personal observations, hyperglycemia can happen during infusions and typically improves afterward. Individuals receiving treatment should be appropriately evaluated, counseled, and reassured.

Surveillance after a Course of Teplizumab Infusion

Teplizumab administration should be considered the first step in altering the natural course of T1D. The median delay in progression from the stage 2 to stage 3 T1D is 32 months from prior clinical trials, and treated individuals must be actively followed over time as they remain at significant risk for progression to stage 3 T1D (Table 2).

- Post-infusion, patients and families should be educated about signs and symptoms of the stage 3 T1D.

Multiple approaches to monitor progression from dysglycemia in stage 2 to overt clinical stage 3 T1D have been proposed [2, 16, 18, 19], and JDRF consensus guidance for monitoring persons with antibody-positive pre-stage 3 T1D is expected to be released soon.

- Providers should consider instituting a surveillance protocol trending OGTT or CGM blood glucose results at least every 6 months for the age group (≥8 year old) the teplizumab is currently approved for, and use threshold values diagnostic for stage 3 T1D [15].

Prescribing insulin for individuals meeting stage 3 T1D criteria solely based on OGTT criteria without clinical signs, such as polyuria, polydipsia, or weight loss, might become a safety concern given high risk of hypoglycemia. There is also a concern (and limited anecdotal evidence) that given high risk of progression to stage 3, these individuals and their families might consider restricting dietary carbohydrates making CGM data less relevant versus OGTT. More studies are needed.

Risk – Benefit Assessment

Given the immune-modifying nature of teplizumab, possibility of serious AEs, and social and economic challenges for the treated individual and their family associated with 14 consecutive days of IV administration,

careful individualized risk-benefit assessment must be performed before treatment is initiated. In a 76-participant study, teplizumab has been shown to delay progression from stage 2 to stage 3 T1D by a median of 32.5 months. To ensure expected benefits are similar in real-world settings to TN-10 outcomes, prescribing physicians should verify that candidates have stage 2 T1D, provide an uninterrupted treatment course, avoid systemic glucocorticoid use unless clinically necessary. Significant variability in response to teplizumab calls for more studies to understand which individuals would benefit most from this treatment and which individuals might have little or no benefit from it. Providers should also familiarize themselves and appropriately counsel potential candidates in stage 2 T1D and their families regarding ongoing clinical trials building upon teplizumab use and exploring other therapeutic options.

Practice Management Considerations and Advocacy

Based on the available evidence and the authors' experience, establishing a teplizumab treatment protocol at a clinical facility necessitates careful consideration of the available services and adherence to established local healthcare system policies and procedures. Initiating the process often involves applying for approval from the healthcare system/hospital pharmacy for teplizumab use. Choosing an infusion location could be a roadblock for facilities lacking a daily open infusion center with weekend access (for more discussions, see above in the Infusion Settings section). Other steps to establish a successful infusion protocol include securing personnel skilled in central line insertions, coordinating laboratory schedules, pharmacy services, and booking the site of infusions. The availability and readiness of visiting nurse services vary across regions, impacting their assistance with infusions and blood draws.

- All team members need training on medication administration and management of adverse reactions.
- The prescribing and/or pediatric diabetes/endocrine on-call physician should be responsible for reviewing laboratory data and evaluating patients for new/ongoing symptoms. Therefore, they must be prepared to manage AEs, including those that develop at home.

Additionally, insurance coverage influences the availability of infusion sites due to cost disparities between outpatient- and hospital-based infusion centers, inpatient facilities, and home-based settings. Reimbursement for tasks associated with teplizumab infusions and monitoring for side effects has been reportedly reassuring for clinicians, who are recommended to negotiate the arrangements with the hospital administration. Persons getting teplizumab often have significant out of pocket expenses for travel, housing, and missed work that may not be covered. More information is needed about how potential lack of insurance coverage for certain groups of patients will affect the practical aspects of teplizumab use as it becomes more frequently prescribed.

- We advocate for universal access to this novel treatment for all high-risk groups including state-insured individuals and those living far from centers with established teplizumab infusion protocols. School-aged children should be provided access to remote learning and transportation support and assistance with living arrangements close to infusion center.

Conclusions and Future Directions

Teplizumab is the first disease-modifying agent to receive FDA approval to delay progression from stage 2 to stage 3 T1D. This summary reflects expert recommendations based on experience from clinical trials, practice, and interpretation of the prescription information to assist diabetes practices in establishing infusion programs.

Given the immunomodulating nature of this novel medication, possibility of AEs, costs and challenges associated with a 2-week infusion course, centers committed to providing such infusions should carefully develop teplizumab infusion programs. Protocols and resources should be established, and the personnel should be trained in every aspect of this treatment, including management of adverse reactions at the infusion facility and after hours.

Hospitals and clinical practices are also urged to establish a robust system of identifying and monitoring patients undergoing teplizumab treatment, acknowledging the need for additional guidance and resources. The diabetes community should continue to advocate for universal access to this therapy for individuals from all socioeconomic backgrounds and ensure coverage by state-based health insurances.

Real-world clinical practice brings variables not accounted for in highly controlled clinical trials. Due to different staging criteria used in the label compared to the

TN-10 pivotal study, the clinically treated population will likely be more diverse from immunologic and metabolic standpoints. In addition, in practice, it may be unavoidable to interrupt infusions, and protocols used for prescreening and monitoring/mitigating the AEs and reactions also will differ between centers. Thus, it is crucial to establish an observational registry to evaluate the effects of real-life variability on safety and efficacy outcomes of teplizumab. Currently, Sanofi, Inc. is set to register adverse effects of medication only. The proposed real-life observational registry would also provide the data on efficacy in diverse populations, as the approval was based on a very small cohort of primarily white individuals.

Teplizumab infusions for individuals at stage 2 represent an important first step in altering the course of T1D. However, these treated patients remain at risk for progression to stage 3, and post-marketing evaluation of both the safety and efficacy will be critical in further informing the T1D community in this treatment strategy. Investigators are continuing efforts to better define those at risk for T1D and to develop even more robust and durable therapies.

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Statement of Ethics

No institutional review board approval was required given the nature of work.

Conflict of Interest Statement

A.R.-L. has been a consultant for Ascendis, BioMarin, BridgeBio. A.R.-L. has been a grant recipient and site-principal investigator for Ultragenyx, Amgen, Ascendis, Takeda. M.J.H. has been a consultant for Sanofi and MannKind and is on the scientific advisory board for SAB Biotherapeutics. E.K.S. has received compensation for educational lectures on diabetes screening from Medscape, the American Diabetes Association, Sanofi, and Health Matters CME, for serving as the Chair of the Steering Committee for Clinical Advances in T1D: Screening, Staging, and Treatment, serving on the Sanofi Drug Agnostic T1D Screening Committee, and consulting for DRI Healthcare and Sanofi. L.A.D. has served on advisory boards for Abata and Vertex and has had clinical trials support to her institution from Dompe, Lilly, Provention Bio, Sanofi, Zealand, and NIH. S.E.G. has served on advisory boards for Abata, Avotres, Genentech, GentiBio, Provention Bio, SAB Biotherapeutics, Sana Biotechnology, and Sanofi. He has also received clinical trial support from Provention Bio and NIH. He serves on data and safety monitoring boards for Diamyd, Juvenile Diabetes Research Foundation, and INNODIA. K.J.G. served as a site PI for commercial clinical trials with teplizumab (Provention Bio and Precigen). K.N.T. served as a site PI for PROTECT clinical trial with teplizumab (Provention Bio).

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Author Contributions

K.N.T., K.J.G., K.M.S., and A.R.-L. have conceived the initial structure of the manuscript. K.N.T., S.M., A.R.-L., N.P., and E.B. have drafted the manuscript. S.E.G., L.A.D., M.H., I.L., and E.K.S. have substantially contributed to the manuscript's design. All authors have critically reviewed the manuscript for important intellectual content, approved the final version, and are accountable for all aspects of the work.

Data Availability Statement

No primary data were collected for this work.

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