T.I.M.E. TO SCREEN

Four steps to help you screen appropriate patients for autoimmune type 1 diabetes (T1D) and identify those that may benefit from disease management before onset of Stage 3 T1D.

T **Trace** familial and medical history

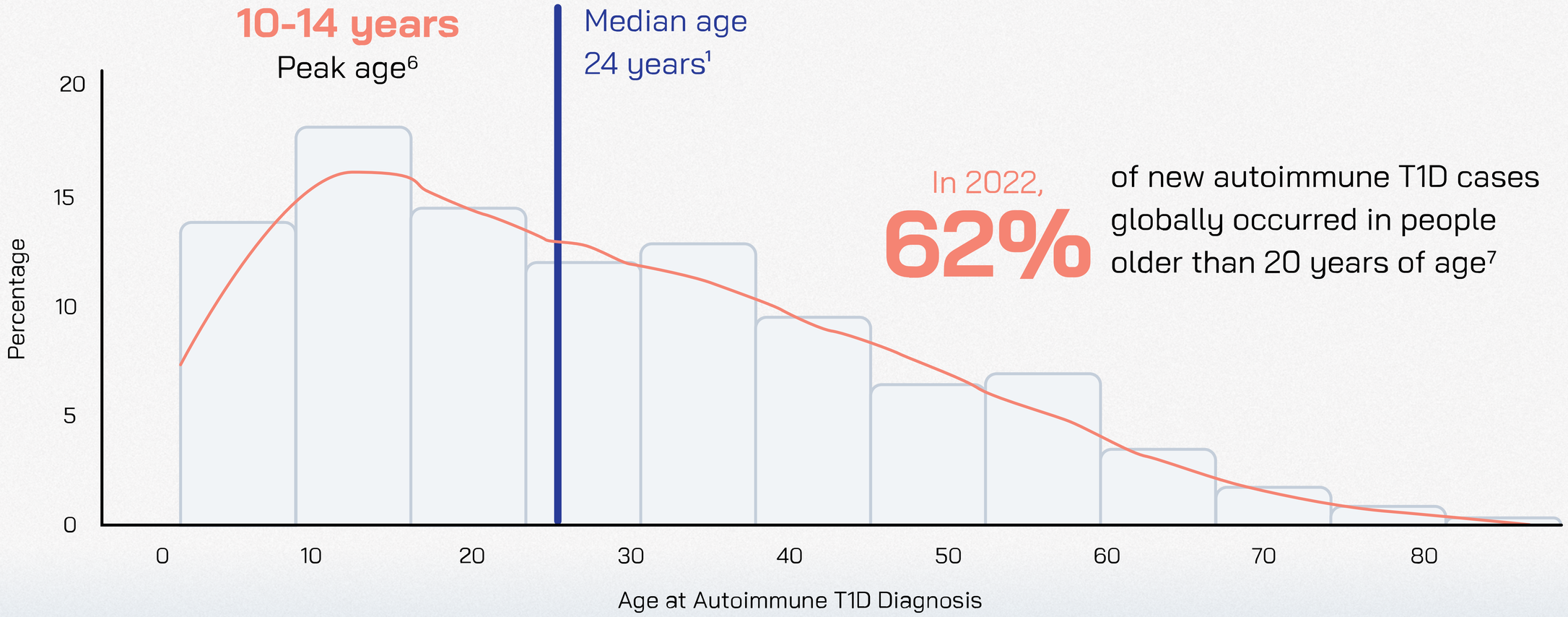
I **Identify** ≥2 pancreatic islet autoantibodies

M **Monitor** blood sugar levels

E **Educate** and motivate patients and caregivers

Type 1 diabetes (T1D) is an autoimmune disease that can affect anyone at any age, regardless of family history[1-3]

Autoimmune T1D results from the destruction of insulin-producing beta cells in the pancreas by the immune system.[4,5] This damage can begin months to years before the onset of symptoms; those at increased risk may not be aware of the beta-cell loss that is occurring.[2]



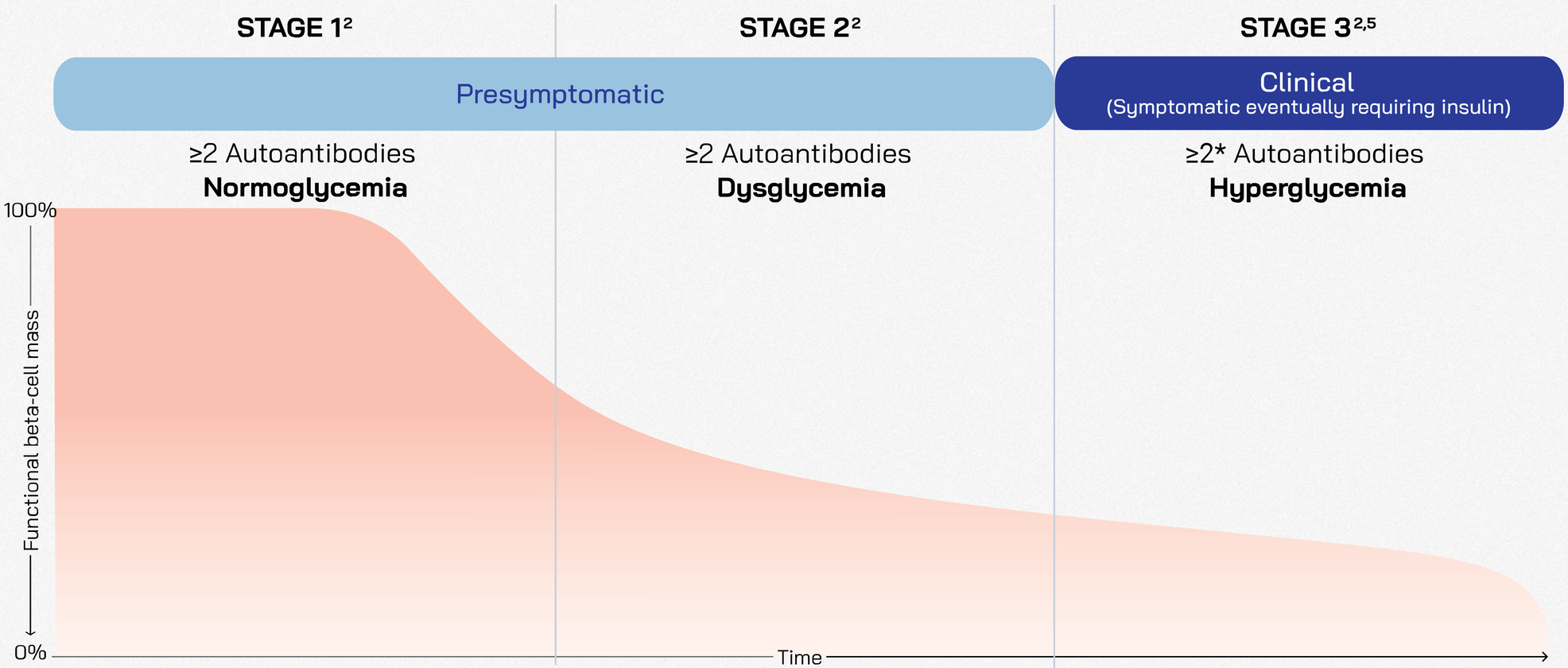
In 2022, **62%** of new autoimmune T1D cases globally occurred in people older than 20 years of age[7]

Distribution of age at diagnosis in US adults with T1D (n=947), National Health Interview Survey (NHIS), 2016 to 2022. Adapted from Fang M. *Ann Intern Med*. 2023.

Up to 60% of people discover they have T1D following diabetic ketoacidosis (DKA), a serious, potentially life-threatening complication.[8-10]

Autoimmune T1D occurs in distinct and detectable stages[2,3]

Autoimmune T1D patients are typically diagnosed in Stage 3 when they have already lost a significant portion of their beta cells.[2]



Risk of progressing to Stage 3 T1D[2]			Risk of progressing to Stage 3 T1D[2]	
5-year risk	10-year risk	Lifetime risk approaches	5-year risk	Lifetime risk approaches
44%	**70%**	**100%**	**75%**	**100%**

*Autoantibodies may become absent at this stage.[4]

Progression from Stage 1 to Stage 3 typically occurs more rapidly the younger a patient is.[2,11]

Trace familial and medical history

Talk to your patients about familial and personal medical history
Family history of autoimmune type 1 diabetes (T1D) and personal or family history of other autoimmune diseases increase the risk of T1D compared with the general population.[3,12]

It's important to screen:

First-degree relatives of T1D patients, who can have a

~15× higher

risk of developing T1D vs the general population.[3]

Those with personal or family history of select autoimmune diseases,

including celiac disease and thyroid disorders such as Hashimoto's or Graves' disease.[12]

Screening for AAbs has been found to reduce DKA at Stage 3 T1D onset by ≥50%.[13,14]

Identify ≥2 pancreatic islet AAbs

Screen for pancreatic islet AAbs
AAb screening is performed to assess autoimmune T1D risk.[3,5]

5 common T1D-related autoantibody tests are[3]:

- Glutamic acid decarboxylase 65 AAb (GADA)
- Insulinoma-associated antigen 2 AAb (IA-2A)
- Insulin AAb (IAA)
- Zinc transporter-8 AAb (ZnT8A)
- Islet cell AAb (ICA)

American Diabetes Association (ADA) recommends testing for 4 AAbs (GADA, IA-2A, IAA, ZnT8A).[4]

When tested together, these 4 have been found to have a 98% autoimmunity detection rate at disease onset.[15]

Patients with 2 or more positive AAbs from the list above should receive additional testing to confirm diagnosis and stage of autoimmune T1D.[5]

Potential considerations if screening test is positive

1 **Talk to your patient and their parent or caregiver to clearly explain next steps, including[16]:**

- A confirmation test
- An evaluation for symptoms of hyperglycemia
- An explanation of islet autoimmunity and autoimmune type 1 diabetes (T1D)

2 **Administer confirmation test[16]:**

Measure all 4 T1D-associated AAbs from a separate serum sample in a CLIA/CAP-certified reference laboratory that has an assay with high specificity and PPV

3 **Evaluate symptoms of hyperglycemia[16]:**

Obtain results from a random blood glucose and HbA1c test to ensure medical safety (prevention of DKA) and aid in the development of a follow-up plan

4 **Explain islet autoimmunity and autoimmune T1D[16]:**

If the confirmation test is positive, have a verbal conversation with the patient, their parent/caregiver, and a provider or staff member who specializes in early autoimmune T1D diagnoses. Discuss:

- Risk for progression to clinical autoimmune T1D
- Frequency of monitoring needed for medical safety
- Options for early intervention

Be mindful of any cultural, language, and socioeconomic barriers in your communication with patients, and encourage them to maintain healthy lifestyles.[16]

Additionally, it's important to discuss the psychological effects of an autoimmune T1D diagnosis on patients and their parents/caregivers (ie, avoidance, anxiety, and distress) and their options for psychological health support.[16]

Currently, there is no widely adopted protocol for screening and monitoring. The appropriate approach for your practice and your patients may vary.

CAP=College of American Pathologists; CLIA=Clinical Laboratory Improvement Amendments; HbA1c=hemoglobin A1C; PPV=positive predictive value.

Monitor blood sugar levels

Dysglycemia is defined as a recurring fluctuation of glucose levels (outside of normal range).[4]

Signs of dysglycemia include[4,17]:

- **FPG** (Fasting plasma glucose) **100-125 mg/dL**
- **2-h PG** (2-hour plasma glucose) during an OGTT **140-199 mg/dL**
- **Intervening plasma glucose** level at 30, 60, or 90 minutes **≥200 mg/dL** during an OGTT
- **A1C 5.7%-6.4% or ≥10%** increase in **A1C**

In patients with ≥2 AAbs, dysglycemia without overt hyperglycemia* indicates Stage 2 autoimmune T1D.[4]

Normal glycemic status[16]:	Dysglycemia or meet any ADA criteria[16]:
Can be managed by their HCP or referred to an endocrinologist.	Individuals can be nonurgently referred to an endocrinologist to discuss management options. Individuals who meet any ADA criteria for clinical autoimmune T1D should be managed by an endocrinologist. Patients' HCPs and endocrinologists should have a verbal conversation prior to referral, as urgent treatment may be needed to avoid DKA.

Glycemic status can inform when to refer individuals with AAbs to endocrinologists.[16]

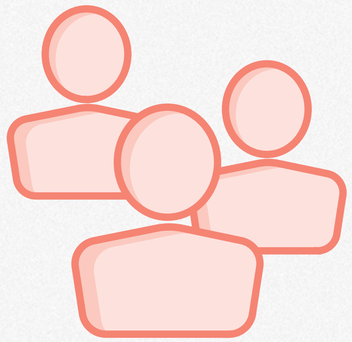
*Overt hyperglycemia means a clear clinical diagnosis could be made (ie, patient in a hyperglycemic crisis or with classic symptoms of hyperglycemia; PG of ≥200 mg/dL) or 2 abnormal screening test results, either from the same sample or in 2 separate test samples. ADA classification ref also used here.[4,5]

OGTT=oral glucose tolerance test.

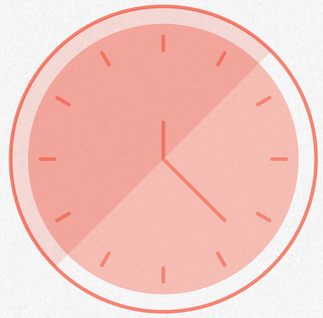
Frequency of monitoring autoimmune type 1 diabetes (T1D) disease progression

The number of AAbs detected, glycemic status, and age may be used to guide frequency of monitoring for progression to clinical T1D.[16]

Key goals for monitoring and management of early-stage autoimmune T1D[16]



- **At-risk individuals and their families should be educated** on the signs and symptoms of diabetes and home blood glucose testing during illness and periodically after their main meals to ensure medical safety
  - **The frequency of blood glucose testing is dependent on age and metabolic status**



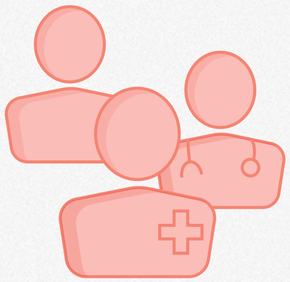
- **HbA1c, OGTT, and/or CGM every 3 to 6 months** may be used to evaluate for progression and staging of autoimmune T1D

If a patient's initial screening is negative for AAbs, screening may be repeated around 6 years of age and, if negative again, around 9 and 11 years of age.[16]

CGM=continuous glucose monitoring.

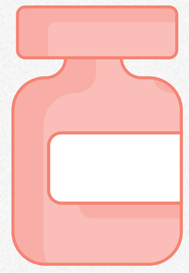
Educate and motivate patients and caregivers

Identifying autoimmune T1D early can give you more time to[5]:



Help assemble your patient's care team by referring them to specialists in a number of areas, including mental health and other support

Advise patients and caregivers to be vigilant for symptoms of hyperglycemia and DKA



Talk to your patients and their care team to know when and how to seek pharmacological intervention if appropriate

T.I.M.E. can help you determine patient eligibility for a potential treatment option.

AAb screening options

TEST		WHERE	ELIGIBILITY	ADA recommended[4] GADA	IA-2A	IAA	ZnT8A	ICA
Commercial Labs[4,5]	Blood draw	• At commercial lab (eg, Labcorp, Quest Diagnostics) or HCP's office • Results shared with patient and provider	• Any individual with a valid script from a licensed HCP • Cost based on insurance coverage	●	●	●	●	●
Online Ordering[18,19]	Finger stick	• Testing kits can be sent by vendors, such as Enable Biosciences • Results shared with both patient and provider	• Any individual regardless of family history of autoimmune type 1 diabetes (T1D) • May be processed and covered through insurance • Those without medical coverage typically pay <$100 out of pocket	●	●	●		
Autoimmunity Screening for Kids (ASK)[20-22] AskHealth.org	Blood draw or finger stick	• At Barbara Davis Center for Diabetes in Aurora or other Colorado locations • At-home screening kits available for families • Results shared with patient with option for provider	• Any individual (age 1 or older) with or without a family history of autoimmune T1D • No out-of-pocket cost	●	●	●	●	
TrialNet[5*†] TrialNet.org/participate	Blood draw or finger stick	• At TrialNet location, event, or health fair • Patient may also administer a kit at home or bring it to Labcorp or Quest Diagnostics • Only patient is notified with results	• Only for those individuals with a family history of autoimmune T1D with certain age restrictions‡ or those who already tested positive through another program • No out-of-pocket cost	●	○	●	○	○

*TrialNet will initially test for 2 autoantibodies. If 1 or more autoantibodies are found in the first test, additional testing may be done for other autoantibodies.
† In screening, a simple blood test is done to screen for the presence of diabetes-related biochemical autoantibodies (GAD and mIAA). Additional autoantibodies ICA, IA-2A, and ZnT8A will also be measured in individuals positive for mIAA. ICA, IA-2A, and ZnT8A will be measured in individuals positive for GAD.
‡Trialnet has an age limit of 2.5-45 years for FDRs and 2.5-20 years for SDRs.
FDR=first-degree relative; mIAA=micro insulin autoantibody; SDR=second-degree relative.

This may not be an exhaustive list of available screening options. The appropriateness of any AAb screening test and the validity of the test results are up to the requesting physician to determine.

Sample codes for testing*

This is a list of autoimmune type 1 diabetes (T1D) codes available as of April 4, 2023; appropriate codes can vary by patient, setting of care, and payer. Determination, verification, and use of correct coding is the sole responsibility of the provider submitting the claim for the item or service. Sanofi does not make any representation or guarantees concerning reimbursement or coverage for any service or item.

ICD-10-CM codes for T1D-related pancreatic islet AAb testing

Description	Code
Diagnosis for T1D	E10.1-E10.9
Encounter for screening for diabetes mellitus	Z13.1
Family history of diabetes mellitus	Z83.3
Family history of other endocrine, nutritional, and metabolic diseases	Z83.49
Endocrine disorder, unspecified	E34.9

CPT® codes for T1D-related pancreatic islet AAb immunoassays

Description	Code
Glutamic acid decarboxylase 65 (GAD) autoantibodies	86341
Insulinoma-associated antigen 2 autoantibody (IA-2A)	
Zinc transporter 8 autoantibody (ZnT8A)	
Islet cell autoantibody (ICA)	
Insulin autoantibody (IAA)	86337

CPT® codes for measuring dysglycemia

Description	Code
Glucose tolerance test (GTT), 3 specimens (includes glucose)	82951
Glucose; quantitative, blood (except reagent strip)	82947
Glucose post glucose dose (includes glucose)	82950
Hemoglobin glycosylated (A1C)	83036

*A specific test code may be required in addition to the CPT code. Please confirm which codes are required for your preferred laboratory.

Commercial lab order codes

These commercial labs offer screening tests and panels that cover ADA-recommended pancreatic islet AAbs.

Scan codes below and enter the appropriate test/panel codes to order for your patients.

Determination, verification, and the use of correct coding is the sole responsibility of the provider submitting the claim for the item or service. Sanofi does not make any representation or guarantees concerning reimbursement or coverage for any service or item.

Quest Diagnostics[23]

Test/panel names	Order codes
GAD65, IA-2, and Insulin Autoantibody	**10584**
Zinc Transporter 8 (ZnT8) Autoantibody	**93022**
Islet Cell Autoantibody Screen with Reflex to Titer	**36741**

Labcorp[24]

Test/panel names	Order codes
Diabetes Autoimmune Profile	**504050**
Antipancreatic Islet Cells	**160721**

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Tzield®
(teplizumab-mzwv)
Injection | 2 mg/2mL

Learn more about a treatment option for your appropriate patients with Stage 2 T1D

INDICATION

TZIELD is a CD3-directed monoclonal antibody indicated to delay the onset of Stage 3 type 1 diabetes (T1D) in adults and pediatric patients aged 8 years and older with Stage 2 T1D.

IMPORTANT SAFETY INFORMATION

WARNINGS AND PRECAUTIONS

- **Cytokine Release Syndrome (CRS):** CRS occurred in TZIELD-treated patients during the treatment period and through 28 days after the last drug administration. Prior to TZIELD treatment, premedicate with antipyretics, antihistamines and/or antiemetics, and treat similarly if symptoms occur during treatment. If severe CRS develops, consider pausing dosing for 1 day to 2 days and administering the remaining doses to complete the full 14-day course on consecutive days; or discontinue treatment. Monitor liver enzymes during treatment. Discontinue TZIELD treatment in patients who develop elevated alanine aminotransferase or aspartate aminotransferase more than 5 times the upper limit of normal (ULN) or bilirubin more than 3 times ULN.
- **Serious Infections:** Use of TZIELD is not recommended in patients with active serious infection or chronic infection other than localized skin infections. Monitor patients for signs and symptoms of infection during and after TZIELD administration. If serious infection develops, treat appropriately, and discontinue TZIELD.
- **Lymphopenia:** Lymphopenia occurred in most TZIELD-treated patients. For most patients, lymphocyte levels began to recover after the fifth day of treatment and returned to pretreatment values within two weeks after treatment completion and without dose interruption. Monitor white blood cell counts during the treatment period. If prolonged severe lymphopenia develops (<500 cells per mcL lasting 1 week or longer), discontinue TZIELD.
- **Hypersensitivity Reactions:** Acute hypersensitivity reactions including serum sickness, angioedema, urticaria, rash, vomiting and bronchospasm occurred in TZIELD-treated patients. If severe hypersensitivity reactions occur, discontinue TZIELD and treat promptly.
- **Vaccinations:** The safety of immunization with live-attenuated (live) vaccines with TZIELD-treated patients has not been studied. TZIELD may interfere with immune response to vaccination and decrease vaccine efficacy. Administer all age-appropriate vaccinations prior to starting TZIELD.
  - Administer live vaccines at least 8 weeks prior to treatment. Live vaccines are not recommended during treatment, or up to 52 weeks after treatment.
  - Administer inactivated (killed) vaccines or mRNA vaccines at least 2 weeks prior to treatment. Inactivated vaccines are not recommended during treatment or 6 weeks after completion of treatment.

ADVERSE REACTIONS

Most common adverse reactions (>10%) were lymphopenia, rash, leukopenia, and headache.

USE IN SPECIFIC POPULATIONS

- **Pregnancy:** May cause fetal harm.
- **Lactation:** A lactating woman may consider pumping and discarding breast milk during and for 20 days after TZIELD administration.

Please read the accompanying Prescribing Information, including patient selection criteria, and Medication Guide.

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