Screening for Pre-Clinical Type 1 Diabetes Mellitus (T1D)

P.J. Zimakas
Pediatric Endocrinology
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THE University of Vermont MEDICAL CENTER

1

FDA NEWS RELEASE

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

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For Immediate Release: November 17, 2022

Diabetes Care
American Diabetes Association

Consensus Guidance for Monitoring Individuals With Islet Autoantibody–Positive Pre-Stage 3 Type 1 Diabetes

Moshe Phillip, Peter Achenbach, Ananta Addala, Anastasia Albanese-O'Neill, Tadej Battelino, Kirstine J. Bell, Rachel E.J. Besser, Ezio Bonifacio, Helen M. Colhoun, Jennifer J. Couper, Maria E. Craig, Thomas Danne, Carine de Beaufort, Klemen Dovc, Kimberly A. Driscoll, Sanjoy Dutta, Osagie Ebekozien, Helena Elding Larsson, Daniel J. Feiten, Brigitte I. Frohnert, Robert A. Gabbay, Mary P. Gallagher, Carla J. Greenbaum, Kurt J. Griffin, William Hagopian, Michael J. Haller, Christel Hendrieckx, Emile Hendriks, Richard I.G. Holt, Lucille Hughes, Heba M. Ismail, Laura M. Jacobsen, Suzanne B. Johnson, Leslie E. Kolb, Olga Kordonouri, Karin Lange, Robert W. Lash, Åke Lernmark, Ingrid Libman, Markus Lundgren, David M. Maahs, M. Loredana Marcovecchio, Chantal Mathieu, Kellee M. Miller, Holly K. O'Donnell, Tal Oron, Shivajirao P. Patil, Rodica Pop-Busui, Marian J. Rewers, Stephen S. Rich, Desmond A. Schatz, Rifka Schulman-Rosenbaum, Kimber M. Simmons, Emily K. Sims, Jay S. Skyler, Laura B. Smith, Cate Speake, Andrea K. Steck, Nicholas P.B. Thomas, Ksenia N. Tonyushkina, Riitta Veijola, John M. Wentworth, Diane K. Wherrett, Jamie R. Wood, Anette-Gabriele Ziegler, and Linda A. DiMeglio

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2

"There is need for primary care to take on some of the early-stage monitoring and managing of [at risk] children and adults. However, staging criteria [of Type 1 diabetes] are relatively new and unlikely to be widely known among primary care health care providers. Therefore, educational steps and materials must facilitate the partnership between primary care providers and secondary care."

3

Objectives

- Outline the potential benefits of screening for pre-clinical Type 1 Diabetes Mellitus (T1D)
- Plan for the appropriate monitoring of children with pre-clinical T1D
- Describe the only approved intervention to delay progression to clinical T1D

4

The W5 of Screening

- **What** are you screening for?
- **What** is the screening test?
- **What** does a positive screening test mean?
- **Why** should you consider screening?
- **Who** should you screen?
- **When** should you screen for this?
- **Where** can you get the screening test?
- **What** do you do with the screening results?

5

Caveat

While there are guidelines for what to do with a positive screening test result for pre-clinical T1D, there are currently no formal guidelines regarding exactly who to screen and when.

6

Disclosures

No financial relationships to disclose

7

What are you screening for?

8

T1D Epidemiology

- ~5-10% of all diabetes cases
- ~1.7 million people in the U.S.
- ~300,000 are less than 20 yo
- One of the most common chronic diseases of childhood
- 0.3% risk of T1D
- Onset typically < 30 years old

9

Diagnosis of T1D

- Typically made at onset of clinical signs and symptoms of hyperglycemia
- Straight forward diagnostic studies:
  - U/A
  - Random glucose
  - A1c
- Insulin therapy is started immediately
- 20-60% of new diagnoses present in DKA

10

Pathogenesis

Genetic Predisposition + Environmental Trigger

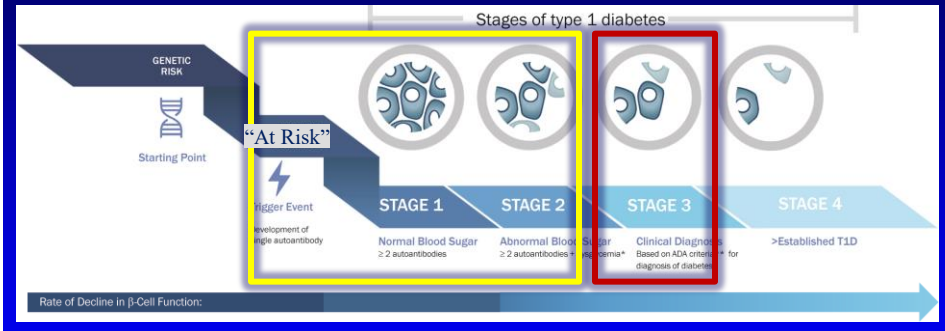
↓

Autoimmune destruction of Beta cells

- Destruction of 50-70% beta cell mass leads to signs and symptoms
- Process takes months to years before clinical diabetes develops

11

Stages of T1D



NIDDK Type 1 Diabetes TrialNet Study Group; Screening for Type 1 Diabetes in the General Population: A Status Report and Perspective. *Diabetes* 1 April 2022; 71 (4): 610–623.

12

What is the screening test?

13

Islet Autoantibodies (IAb)

- Islet autoantibodies (IAb): autoantibodies that recognize proteins associated with the pancreatic Beta cell
- 4 principal islet autoantibodies (IAb):
  - Insulin autoantibody (IAA)
  - Glutamic acid decarboxylase-65 (GAD65)
  - Insulinoma-associated protein 2 (IA-2)
  - Zinc transporter (ZnT8)

14

Table 3—Autoantibodies against islet autoantigens detected in stage 1–3 type 1 diabetes

Autoantibody	Islet specificity	Typical characteristics
IAA	Insulin	• Common as a first detected autoantibody in young children (157,158) • Appearance is more common in younger children (159) • Frequency of appearance declines with age • Not informative for individuals treated with insulin, who often develop antibodies in response to injected insulin
GADA	GAD	• Common as a first detected autoantibody in childhood, up until age 15 years (157,158,160) • Adult-onset cases most often present with GADA (161) • Is associated with slower progression to T1D (162) and is often found as a single positive islet autoantibody, especially in adults
IA-2A (also known as ICA512)	Tyrosine phosphatase islet antigen-2	Presence is associated with more advanced islet autoimmunity and faster progression to stage 3 T1D (55,163)
ZnT8A	Zinc transporter type 8, a transmembrane protein in the β-cell granule	Presence can improve risk stratification in individuals with single $GADA^+$, IAA^+, or $IA\text{-}2A^+$ status (164)

IA-2A, insulinoma antigen-2 autoantibody; ICA, islet cell autoantibodies; ICA512, islet cell autoantigen 512; T1D, type 1 diabetes.

Moshe et al.; Consensus Guidance for Monitoring Individuals With Islet Autoantibody–Positive Pre-Stage 3 Type 1 Diabetes. *Diabetes Care* 25 July 2024; 47 (8): 1276–1298.

15

The Screening Test

- Islet autoantibody (IAb) screening:
  - Minimal blood volume required
  - Minimally invasive:
    - Can be capillary and dried bloodspots
    - Can be collected at home or in the community

16

What does a positive screen mean?

17

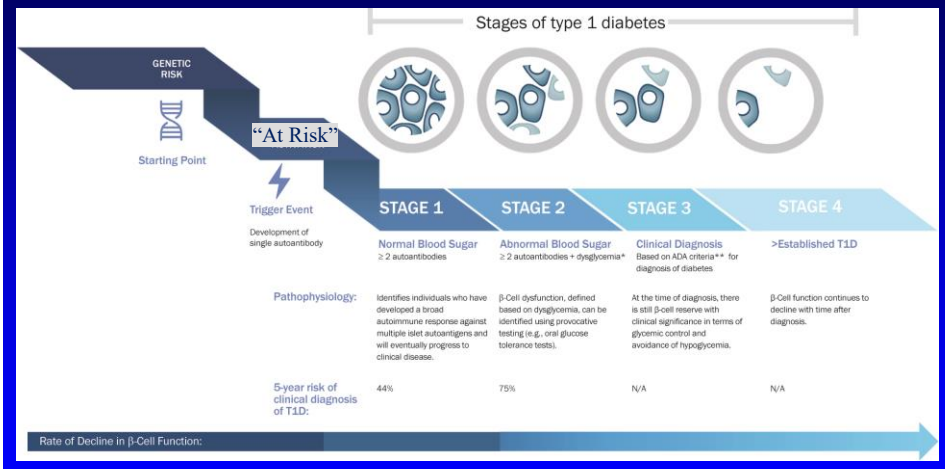
What do IAb+ mean?

Islet autoantibody positive (IAb+)

- Identifies risk for progression to clinical (Stage 3) T1D

18

Stages of T1D



NIDDK Type 1 Diabetes TrialNet Study Group; Screening for Type 1 Diabetes in the General Population: A Status Report and Perspective. *Diabetes* 1 April 2022; 71 (4): 610–623.

19

Stages of T1D

	"At Risk"	Stage 1	Stage 2	Stage 3
Beta cell autoimmunity	Single IAb+	≥2 IAb+	≥2 IAb+	≥1 IAb+
Symptoms	no	no	no	yes
Blood glucose levels	normoglycemia	normoglycemia	dysglycemia	hyperglycemia meeting Diabetes criteria

IAb+ = positive islet autoantibody

20

Glycemic Status

Test	Normoglycemia	Dysglycemia	Diabetes
Fasting glucose	< 100 mg/dL	100-125 mg/dL	≥ 126 mg/dL
2 hour OGTT (oral glucose tolerance test)	< 140 mg/dL	140-199 mg/dL	≥ 200 mg/dL
Random glucose	< 140 mg/dL	140-199 mg/dL	≥ 200 mg/dL
HbA1c	<5.7%	5.7-6.4%	≥ 6.5%

21

Risk of a Single IAb+

- Risk of progressing from single IAb+ to multiple IAb+ is highest in the first 2 years following seroconversion
- Up to 50% of children with single IAb+ revert to being antibody negative

22

Risk

	Risk for progression to Stage 3		
	5-year	15-year	Lifetime
Single IAb+ that reverts – within 2 years		12%	
Single IAb+ that persists after 2 years		30%	
Single IAb+ that goes on to multiple IAb+ by 2 years		82%	

23

Risk of a Multiple IAb+

- Lifetime risk of progressing Stage 3 T1D is >99%
- < 4% of individuals with multiple antibodies will revert to negative antibodies

24

Risk

	Risk for progression to Stage 3		
	5-year	15-year	Lifetime
Stage 1 ≥2 IAb+, normoglycemia	44%	80-90%	
Stage 2 ≥2 IAb+, dysglycemia	75%	>90%	100%

25

What do IAb+ mean?

Islet autoantibody positive (IAb+)

- Identifies risk for progression to clinical T1D
- But the speed of progression between stages is quite variable from person to person
- Highest risk for progression is:
  - Seroconversion <2 years old
  - High IA-2 autoantibody
  - 3 or more autoantibodies

26

Why should you consider screening?

27

Goals of Screening

1. Prevent DKA and it's associated short- and long-term morbidity and mortality

28

DKA at clinical diagnosis

- Ranges from 20-60% in North America
- DKA:
  - the leading cause of morbidity/mortality in children with T1D
  - case fatality rate of ~0.3%
  - clinically significant cerebral edema occurs in ~0.6%
    - mortality rate of 20-25%
    - morbidity: 20-25% of survivors have permanent neurologic sequelae

29

DKA at clinical diagnosis

- Without screening: 20-60%
- With screening: 2-5%
- Accomplished by:
  - patient/caregiver education regarding risk and symptoms to watch for
  - periodic monitoring for early detection of progression to stage 3

30

Screening

1. Prevent DKA and it's associated short- and long-term morbidity and mortality
2. Minimize requirement for ER, hospitalization, ICU at time of stage 3 T1D
3. Advance preventative therapies through clinical trial recruitment
4. Offer interventions to delay progression to stage 3 T1D

31

Who should you screen?

32

Who to Screen

General population (everybody and anybody)

vs

Targeted (first +/- second degree family members)

33

General Population Screening

- ~90% of individuals with newly diagnosed T1D do NOT have a family history of the disease
- Therefore, to identify the most individuals who would benefit from therapies to delay or prevent Stage 3 T1D, those without a positive family history must be identified

34

Who to screen

- Majority of data collected is derived from studies involving 1st degree relatives
- Data regarding general population screening is more limited

35

Targeted Screening

- Individuals with a first-degree relative with T1D:
  - have ~15x increased relative lifetime risk compared to the general population
  - Prevalence by 20 years of age is ~5% compared with ~0.3%

36

When should you screen?

37

Optimal Age for Screening

- Many individuals seroconvert to IAb+ by 2-3 years of age
- Sensitivity of autoantibody screening between 3–5 years is 35%
- Can be improved up to 80% with repeated screening at both 2–3 years and 5–7 years
- Some propose screening the NBS dry spots for genetic risk factors and then antibodies as often as annually

38

Optimal Age for Screening

- At this time:
  - Screening should be initially considered in first degree relatives between 2-3 years of age and repeated between 5-7 years age
  - Or should be offered at any point in an older aged child/adolescent/young adult with a new family history of T1D

39

Where can you get the screening test?

40

Autoantibody Test Code	
All 4 IAb can be ordered via Quest Diagnostics: Type 1 Diabetes Autoantibody Panel	Quest Test Code: 13621
Individual Autoantibody Test Codes	
Insulin Autoantibody (IAA)	CPT 86337
Glutamic Acid Decarboxylase (GAD)	CPT 86341
Islet Antigen 2 (IA-2)	CPT 86341
Zinc Transporter 8 (ZnT8)	CPT 86341
Related Diagnosis Codes	
Family History of Diabetes Mellitus	Z83.3
Screening for Diabetes Mellitus	Z13.1
Type 1 Diabetes, Presymptomatic, Unspecified	E10.A0
Type 1 Diabetes, Presymptomatic, Stage 1	E10.A1
Type 1 Diabetes, Presymptomatic, Stage 2	E10.A2

41

TrialNet
www.trialnet.org

Type 1 Diabetes TrialNet

Will provide free screening if:

- between the ages of 2 to 45 years and have a parent, brother/sister, or child with T1D
- between the ages of 2 to 20 years and have an aunt/uncle, cousin, grandparent, niece/nephew, or half-sibling with T1D
- between the ages of 2 to 45 years and have tested positive for at least one T1D related autoantibody outside of TrialNet

42

TrialNet
www.trialnet.org

Screening options:

- Test at one of their clinical sites (closest is Boston)
- Home kit: This free kit provides everything you need to collect a finger-stick blood sample at home. Ship it back free using FedEx
- Lab kit: Can take this free screening kit to any Quest Diagnostics or LabCorp lab for a blood draw.

43

TrialNet
www.trialnet.org

- Results available in 4-6 weeks and delivered directly to the patient
- If negative, results delivered by mail
- If positive, they call patient to review next steps

44

TrialNet
www.trialnet.org

If 2+ autoantibodies are detected:

- Patients are offered the option to enroll in monitoring protocol
- Invited to come to a TrialNet location once or twice a year for follow up
- Visits will include metabolic staging and monitoring tests
- They will also be informed regarding different research studies available for early stage T1D

45

A.S.K.
www.askhealth.org

Autoimmunity Screening for Kids

- Run through University of Colorado Barbara Davis Center
- Screening includes both IAb screening for T1D and TTG screening for Celiac disease
- Program offers universal free screening of all U.S. residents, regardless of family history

46

A.S.K.

www.askhealth.org

Autoimmunity Screening for Kids + Parents!
ask
A SIMPLE TEST TO DETECT
Type 1 Diabetes (T1D) + Celiac

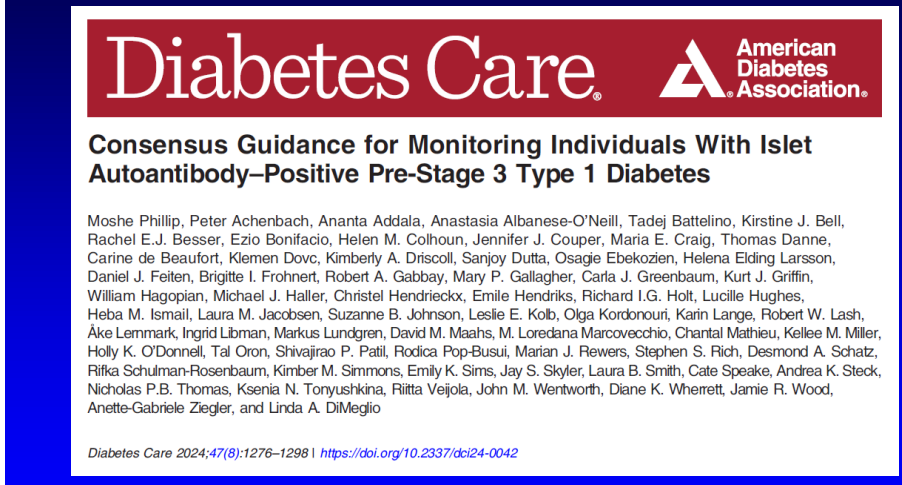
Screening options:

- Test at their clinical sites (only in Colorado)
- Home kit: This free kit provides everything you need to collect a finger-stick blood sample at home. Ship it back free using FedEx
- Lab kit: Can take this free screening kit to any LabCorp lab for a blood draw.

47

What do you do with a positive screening test?

48



49

Primary Care Expectations

- PCPs should understand the stages of T1D as well as suggested frequency of metabolic monitoring that can be used to prevent DKA at onset of clinical Stage 3 T1D
- PCPs with a specific interest in managing people with early stage T1D can serve as a local referral resource for other PCPs when specialist care providers are not readily accessible
- PCP and specialty care provider, along with patient and family, should determine which provider will have primary responsibility for metabolic monitoring and what degree of collaboration is desired
- Level of specialist engagement will need to be reassessed and may shift over time as patient progresses through the stages of T1D

50

Monitoring of Single IAb+

- Confirm initial results with repeat sample within 3 months
- IAb and metabolic monitoring during the first 2 years after seroconversion is the most critical

51

Monitoring of Single IAb+

- < 3 yo: repeat IAb and metabolic monitoring (random BG and A1c) q 6 months for 3 years and then annually for another 3 years
- ≥3 yo: repeat IAb and metabolic monitoring (random BG and A1c) annually for 3 years and then stop if remains unchanged or reverts to negative
- Regular education regarding signs and symptoms of hyperglycemia and DKA

52

Monitoring of Multiple IAb+

- Confirm initial results with repeat sample within 3 months
- Baseline glycemic testing to establish stage of T1D

53

Glycemic Staging

Oral Glucose Tolerance Test (OGTT)

- Gold standard test for preclinical T1D staging
- Oral glucose load 1.75g/kg (75g max)
- Fasting and 2h post blood glucose levels

54

Glycemic Staging

Test	Stage 1 Normoglycemia	Stage 2 Dysglycemia	Stage 3 Diabetes
Fasting glucose	< 100 mg/dL	100-125 mg/dL	≥ 126 mg/dL
2 hour OGTT (glucose tolerance test)	< 140 mg/dL	140-199 mg/dL	≥ 200 mg/dL

55

Glycemic Staging

HbA1c

Test	Stage 1 Normoglycemia	Stage 2 Dysglycemia	Stage 3 Diabetes
A1c	< 5.7%	5.7-6.4%	≥ 6.5%

- Less reliable in young children and falsely normal in conditions that affect erythrocyte turnover (like hemoglobinopathy)
- Markers of increased risk for progression:
  - 10% rise in A1c on two consecutive tests collected 3-12 months apart

56

Glycemic Staging

Random venous glucose

- Poor sensitivity but good specificity

Continuous glucose monitoring

- 10% time spent at >140 mg/dl had an 80% risk of progression to Stage 3 T1D over 1 year (91% specificity, 88% sensitivity)

57

TABLE 1 Monitoring tools in children with multiple islet autoantibodies

Metric	Pros	Cons	Information gained
OGTT	Gold standard Used to stage disease and predict progression	Requires glucose load and 2 to 5 blood draws over 2 h	Glycemic staging Risk scores for progression (DPTRS, DPTRS60, Index60, M120)[66–70]
Random venous glucose	One-off sample Low cost	Requires a blood draw	Similar to 2-h OGTT-derived glucose[71]
HbA1c	Highly specific Can use capillary sample	Insensitive, often normal in asymptomatic or recent onset Stage 3 diabetes, may be affected by disease states*	Risk of progression to "clinical disease": HbA1c >5.7%, or 10% rise over 3–12 months[75]
CGM	Use at home	Optimal duration and frequency of CGM wear not yet determined. Cost and access issues.	Risk of progression to "clinical disease": 10% > 7.8 mmol/L (>140 mg/dl)[76] Realtime monitoring over 24 h
Self-monitoring blood glucose	Simple use at home	Optimal timing and frequency have not been determined, unconfirmed glucose values	Immediate result

Besser et al. ISPAD Clinical Practice Consensus Guidelines 2022: Stages of type 1 diabetes in children and adolescents. Pediatr Diabetes. 2022 Dec;23(8):1175-1187.

58

Monitoring of Stage 1 T1D

- Document clearly in chart
- HbA1c and random blood glucose monitoring:
  - <3 yo: q 3 months
  - 3-9 yo: q 6 months
  - >9 yo: q 12 months

59

Monitoring of Stage 2 T1D

- Document clearly in chart
- Referral to endocrinology
- HbA1c and random blood glucose monitoring q 3 months
- Monitor for symptoms, weight trends
- Discuss option of teplizumab, if eligible

60

Monitoring of Stage 2 T1D

- Consider home glucometer (measure 2 postprandial blood glucose on different days, every 1-3 months)
- Consider 10 days of CGM every 3 months

61

Education of IAb+ Individuals

- Education should be provided:
  - At the initial positive IAb screen
  - At diagnosis of each stage
  - Annually for review

62

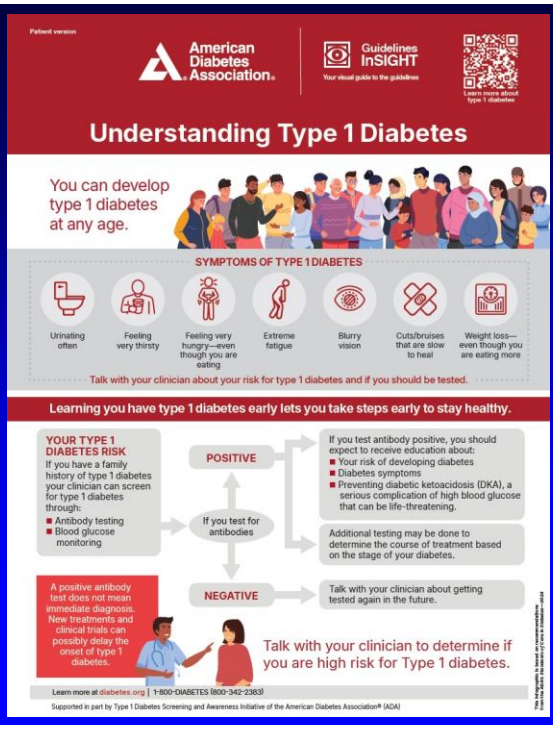
Education of IAb+ Individuals

Topics to be discussed:

- Significance of each stage regarding risk of progression
- Signs and symptoms of hyperglycemia and DKA

63

ADA T1D Toolkit
121724_T1D_Toolkit.pdf



64

Education of IAb+ Individuals

Topics to be discussed:

- Significance of each stage regarding risk of progression
- Signs and symptoms of hyperglycemia and DKA
- Who to contact and when
- Eligibility criteria for early intervention therapy
- Resources for exploring and understanding benefits of participation in research studies

65

Interventions

- Primary prevention
  - Preventing seroconversion to IAb+ in genetically at risk
- Secondary prevention
  - Preventing progression to Stage 3
- Intervention
  - Slowing progression of Stage 3

66

Teplizumab

- First and only therapeutic agent approved for delaying the onset of stage 3 T1D
- FDA approved for:
  ≥ 8 yo and with stage 2 T1D

67

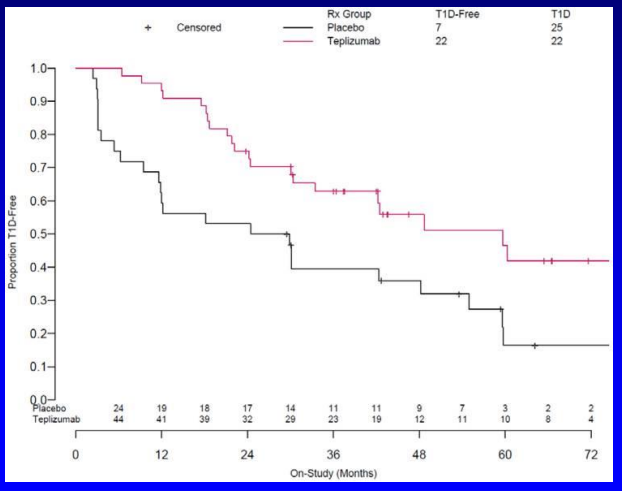
Teplizumab

- Humanized anti-CD3 monoclonal antibody
- Administered as a single 14-day course of daily intravenous infusions

68

Teplizumab

- Landmark prevention trial:



Sims et al. Type 1 Diabetes TrialNet Study Group. Teplizumab improves and stabilizes beta cell function in antibody-positive high-risk individuals. Sci Transl Med. 2021 Mar 3;13(583)

69

Teplizumab

- Landmark prevention trial:
  - At the end of the study, 50% of teplizumab remained stage 2 vs only 22% of the placebo group
  - 47% risk reduction for progression to stage 3 during the study period
  - Delayed progression to stage 3 by a median time of 2 years 8 months

70

Teplizumab

- Side effect: transient lymphopenia (self resolving), rash, headache, transient liver transaminase elevation, and nausea, rarely causes cytokine release syndrome

71

Teplizumab

- Delaying stage 3 T1D by two and a half years (on average) means:
  - 3,700+ fewer injections
  - 3,700+ fewer finger sticks
  - 300–350 fewer infusion set changes
  - 70–130 fewer continuous glucose monitors changes

72

Psychological Burden

- Positive genetic and islet autoantibody screening results are associated with increased parental stress
- Sources of stress:
  - Unpredictable time course: for those with early stage T1D, the latency period may last years
  - Imposing disease monitoring burden
  - Up until recently – no approved early intervention therapy

73

Psychological Burden

- Fortunately, this stress appears to decline rapidly within 3 to 12 months of the results
- Early education and counseling can produce effective results
- Also, tend to have reduced stress overall reported at the time when insulin therapy is needed

Johnson et al. My child is islet autoantibody positive: impact on parental anxiety. Diabetes Care. 2017;40(9):1167-1172

Ziegler et al. Yield of a public health screening of children for islet autoantibodies in Bavaria, Germany. JAMA. 2020;323(4):339-351

74

Psychological Burden

- Assessment should occur at regular intervals, since reactions are likely the change over time, particularly as a patient ages
- Family context and prior experience with T1D are important considerations when assessing psychosocial impact and need for additional support

75

76