1

Type 1 Diabetes: A New Breakthrough in Therapy

Thomas Repas, DO
Endocrinology, Diabetes, and Metabolism; Clinical Lipidology; Nutrition; & Internal Medicine
Campbell County Health
Gillette, WY

2

Disclosures

I have no conflicts of interest to disclose relating to any pharmaceutical manufacturer, research sponsor, or other commercial entity

However, when reviewing the history of type 1 diabetes research, I will describe some of the past experimental attempts at prevention and/or reversal of type 1 diabetes which were never approved by the FDA – and I will disclose them as such

3

Disclosures to Participants

Notice of Requirements for Successful Completion:

Learners must participate in the full activity and complete the evaluation in order to claim continuing education credit/hours.

Presenter has No - Conflicts of Interest/Financial Relationships Disclosures:

Dr. Tom Repas, DO, FACE

Disclosure of Relevant Financial Relationships and Mechanism to Identify and Mitigate Conflicts of Interest: No conflicts of interest

Non-Endorsement of Products: Accredited status does not imply endorsement by ADCES or Joint Accreditation of any commercial products displayed in conjunction with this educational activity

Off-label Use: None

4

4

Objectives

1. Review the pathogenesis of type 1 diabetes, including genetic risk, beta cell autoimmunity, and the stages of type 1 diabetes
2. Discuss screening for future risk of developing type 1 diabetes
3. Review past attempts at modulating beta cell autoimmunity and/or sustaining beta cell function
4. Discuss a newly FDA approved treatment for delaying progression of type 1 diabetes to stage 3

5

Classification of Diabetes Mellitus

- Pre-diabetes - blood glucose levels that are higher than normal, but not high enough to be diagnosed as diabetes
- Type 1 diabetes - a disease resulting from destruction to the pancreatic beta cells, which ultimately results in absolute insulin deficiency
  - Type 1A diabetes – from autoimmune destruction to the pancreatic beta cells, which ultimately results in absolute insulin deficiency
  - Type 1B diabetes – near-complete loss of beta cell function due to a non-autoimmune pathophysiologic process
- Type 2 diabetes - results from a complex process, the classic type 2 diabetic has years or even decades of insulin resistance followed by relative beta cell failure and finally overt diabetes
- Gestational diabetes - hyperglycemia from the insulin resistance and hormonal changes during pregnancy
  - Up to 60% develop type 2 diabetes in their lifetime
- Other types - genetic and secondary forms of diabetes

Balasubramanyam A Classification of diabetes mellitus and genetic diabetic syndromes. Up to Date

6

Type 1A Diabetes

- Caused by a combination of factors including genetic predisposition, environmental triggers, and autoimmune beta cell destruction
- Autoimmune disease often seen in association with other autoimmune disorders
- Progressive destruction of beta cells over months and years
  - Eventually leading to absolute insulin deficiency
- Acute onset of overt type 1 diabetes (DM1) can be sudden, even though the progression may have slow
  - Extreme thirst, weight loss, extreme fatigue, and elevated glucose levels
- All people with type 1 DM require life long insulin to survive

Until recently current therapies focused on metabolic control and prevention of complications- rather than modifying the autoimmune process

7

Type 1A Diabetes

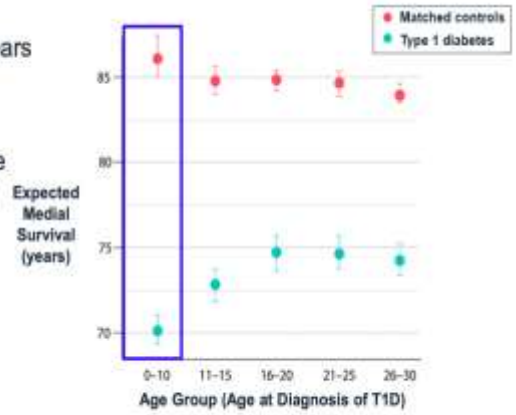
- New-onset type 1 diabetes may occur at any age
  - Classic type 1 diabetes is often thought of as a disorder of childhood or young adulthood…*BUT*
  - About half of all type 1 diabetes is diagnosed after age 30[1]
- Incidence is increasing ~ 2% per year in patients aged < 20 years
  - ~ 1.6 million Americans living with DM1
  - ~ 64,000 people diagnosed each year
- Adults represent 85% of the total population with type 1 diabetes[2]
  - Adult onset type 1 is often mistaken for type 2 diabetes
  - Adult onset type 1 are thinner and often do not have features of insulin resistance compared to DM2
  - Adult onset type 1 frequently have other autoimmune disorders (eg thyroid, celiac, RA, etc)

FYI: just because someone has overweight/obesity, or they are older- does not rule out possibility of having type 1 diabetes

8

Diagnosis of DM1 in Childhood has Negative Effects upon Survival

- Incidence greatest at 10 – 14 years of age[1]
- Many diagnosed before age 14
- T1D associated with reduced life expectancy[2]
  - 16-year reduction when diagnosed by age 10
  - 10-year reduction when diagnosed after age 10



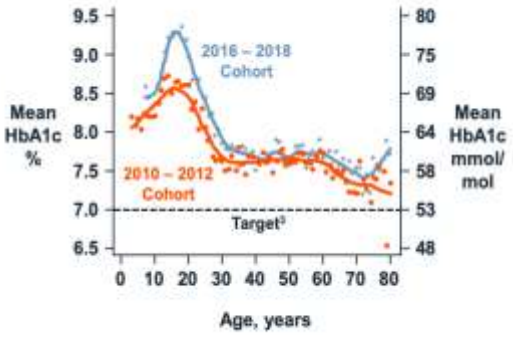
1. Rogers, 2017; 2. Rawshani, 2018

From: https://www.fda.gov/media/149543/download

9

Achieving Optimal Control Remains Challenging

- Despite improvements in insulin technology
- Only 17 – 23% of children, 30% of adults reach desired glycemic ranges[1]
- Glycemic control worst in 15 – 18 age group, establishing high glycemic legacy early in life[2]



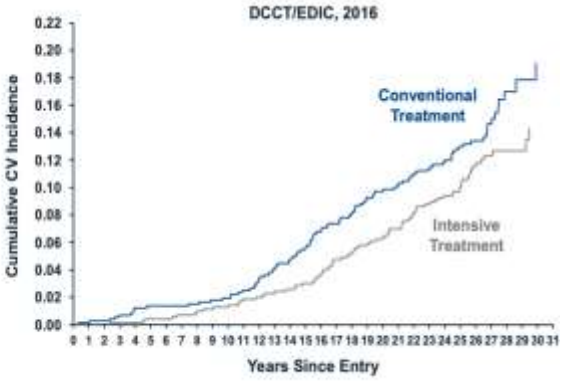
1. Miller, 2015; 2. Foster, 2019; 3. Diabetes Care, 2018

From: https://www.fda.gov/media/149543/download

10

Poor Glycemic Control Early on in Diagnosis has Negative Long Term Effects

- Lower HbA1c for 6.5 years in DCCT/EDIC reduced
  - CV events by 30% after 30 years
  - Microvascular events by 35 – 76% after 30 years[1]



Dubitoxi-Klug, 2016; 1. Nathan, 2014
DCCT: Diabetes Control and Complications Trial, EDIC: Epidemiology of Diabetes Interventions and Complications

From: https://www.fda.gov/media/149543/download

11

There is a Need for Interventions to Delay or Prevent Type 1 Diabetes

Preventing or delaying the progression of type 1 diabetes could have the following benefits

- Maintain near normal glycemic control for the first several years free from lifestyle restrictions, risk of ketoacidosis, or fear of hypoglycemia
- Reduce the number of young people dependent on insulin during childhood through adolescence
- Provide excellent control for the first several years, may reduce long term complications
- Achieve improved glycemic control with little burden of patient compliance beyond only the first few weeks/months

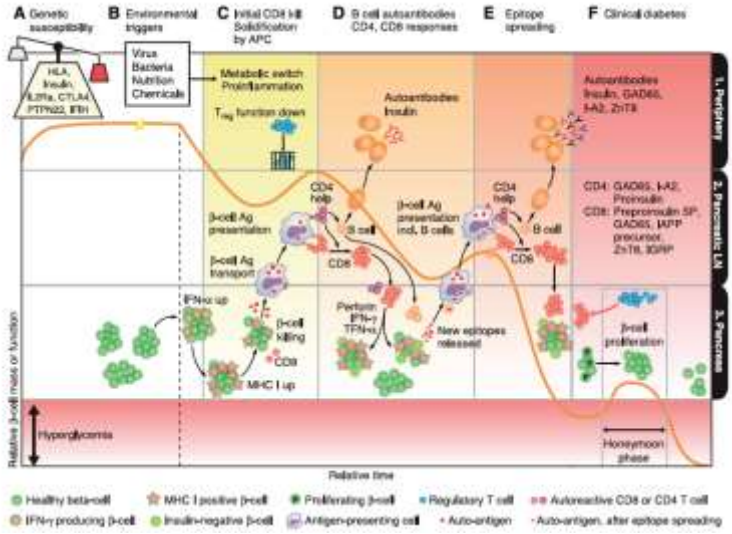
From: https://www.fda.gov/media/149543/download

12

Pathogenesis of Type 1 Diabetes

13

How Type 1 Diabetes Might Arise



14

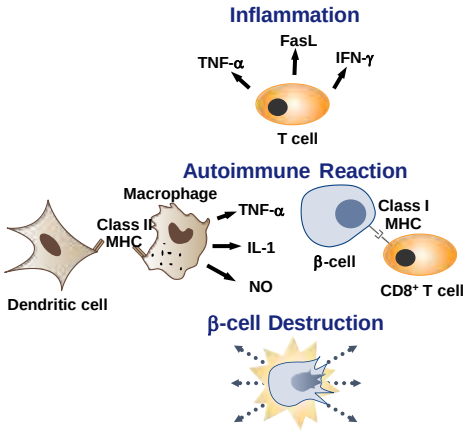
van Belle TL, et al. *Physiol Rev.* 2011;91:79-118.

14

Type 1 Diabetes Pathophysiology

β-cell destruction- usually leading to absolute insulin deficiency as a result of:

1. Genetic predisposition
2. Environmental trigger
3. Autoimmunity
4. Other/unknown factors



CD8, cluster of differentiation 8; FasL, Fas ligand; IFN-γ, interferon γ; IL-1, interleukin 1; MHC, major histocompatibility complex; NO, nitric oxide; TNF-α, tumor necrosis factor α.

Maahs DM, et al. *Endocrinol Metab Clin North Am*. 2010;39:481-497.

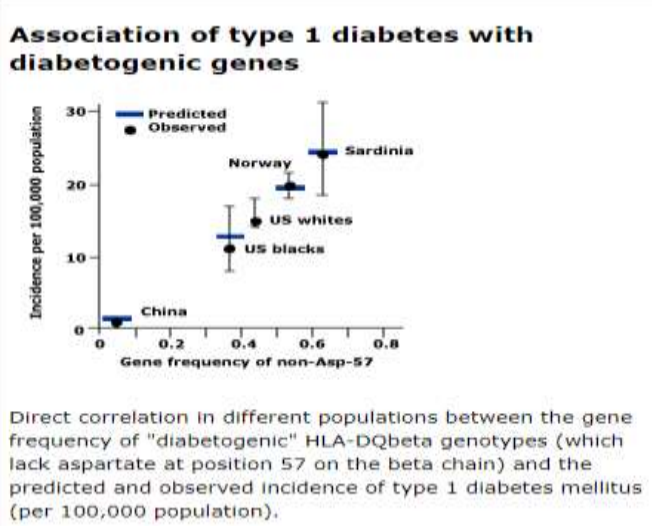
15

Pathogenesis –Genetic-

- Genetic susceptibility: there are major susceptibility genes (MHC) for DM1 in the HLA region on chromosome 6p
  - 90% of patients with type 1 diabetes have either DR3-DQ2 or DR4-DQ8 but only 40% of non-DM control group (30% of DM1 have both)
  - DQB1*0602 protects against the development of type 1 diabetes

Hirsch I. Pathogenesis of type 1 diabetes mellitus. Up to Date
Dahlquist GG, et al Diabetes Care. 1999;22(10):1698.
Dorman JS, et al. Proc Natl Acad Sci USA 1990; 87:7370.

Pathogenesis –Genetic-



Direct correlation in different populations between the gene frequency of "diabetogenic" HLA-DQbeta genotypes (which lack aspartate at position 57 on the beta chain) and the predicted and observed incidence of type 1 diabetes mellitus (per 100,000 population).

Hirsch I. Pathogenesis of type 1 diabetes mellitus. Up to Date
Dorman JS, LaPorte RE, Stone RA, Trucco M, Worldwide differences in the incidence of type I diabetes are associated with amino acid variation at position 57 of the HLA-DQ beta chain. Proc Natl Acad Sci USA 1990; 87:7370.

17

Family History and Risk of Developing T1D

- **The lifetime risk of developing Stage 3 T1D is up to 15x higher than the general population for any first-degree relatives of current T1D patients**[3,4]
- *A child's risk is doubled if a parent developed Stage 3 T1D before age 11.*[4]

From: https://connectedbyt1d.com/t1d-risk

18

Family History and Risk of Developing T1D

From: https://connectedbyt1d.com/t1d-risk

19

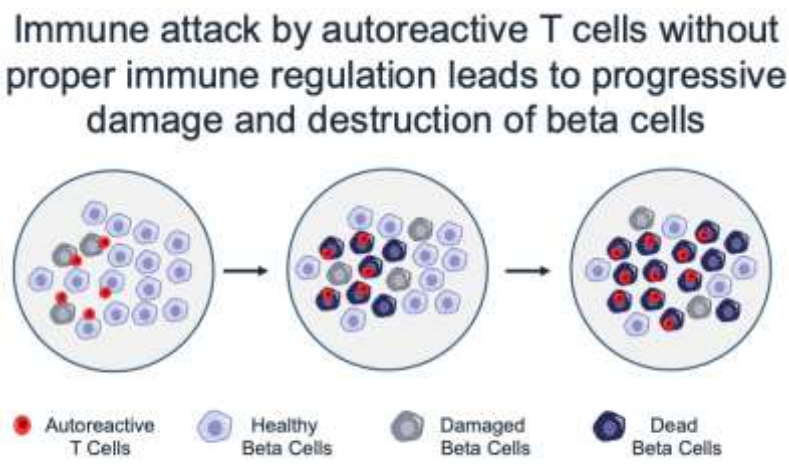
Pathogenesis –Environmental Factors-

- Environmental factors often are also a factor in causing DM1 to develop in predisposed individuals
  - Perinatal- maternal age >25 years, preeclampsia, neonatal respiratory disease, and jaundice increase risk- while low birth weight and short birth length are protective
  - Viruses- Coxsackie virus antibody titers higher in pregnant women whose children developed type 1 diabetes. Enteroviral infections were ~2x more common in siblings who developed DM1
  - Cows milk- a few studies showed association with early introduction of cow's milk, while most other studies did not show such association
  - Cereals- first exposure to cereal before age 3 months vor after 7 months was associated with an increased risk of developing beta cell autoantibodies
  - Other- the hygiene theory proposes increase risk of autoimmune disorders.

Hirsch I. Pathogenesis of type 1 diabetes mellitus. Up to Date
Virtanen SM, et al. Diabetologia. 1994;37(4):381.
Hummel M, et al. Diabetes Care. 2000;23(7):969.
Norris JM, et al JAMA. 2003;290(13):1713.

20

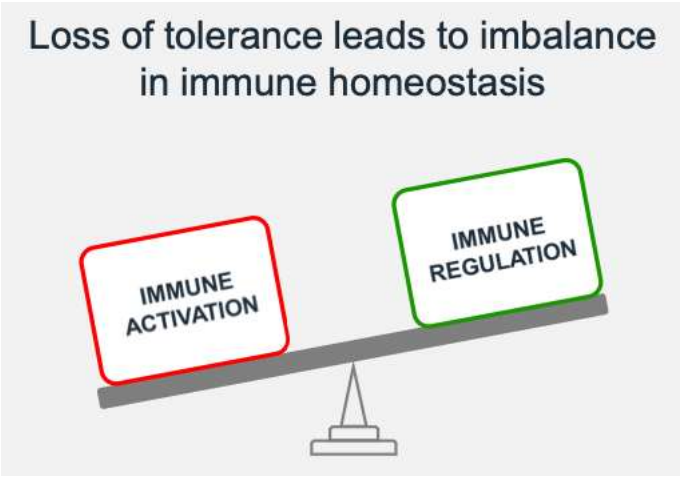
Pathogenesis –Autoimmunity-



From: https://www.fda.gov/media/149543/download

21

Pathogenesis –Autoimmunity-



From: https://www.fda.gov/media/149543/download

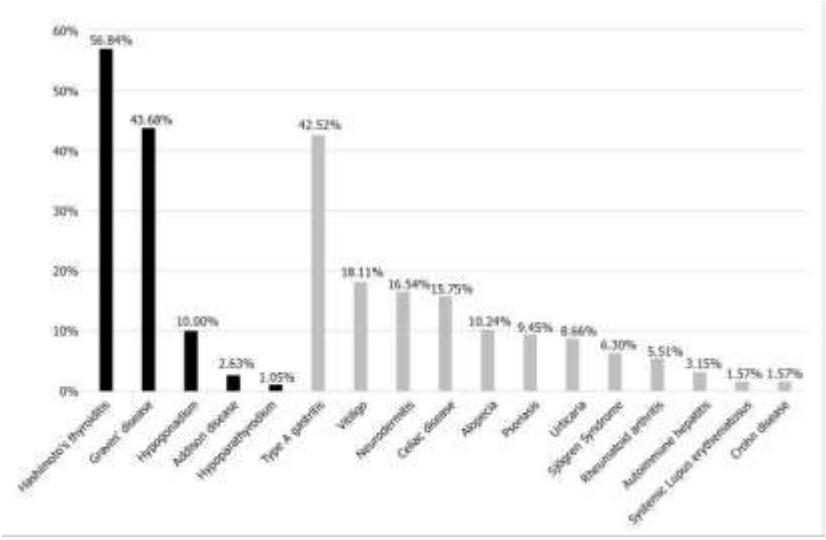
22

Type 1 diabetes and Associated Autoimmune Disorders

- 491 children diagnosed with type 1 diabetes at the Barbara Davis Center for Childhood Diabetes were screened for other associated autoimmune disorders
  - 24.8% were positive for TPO Ab, with 12.3% of those having autoimmune thyroid disease.
  - 11.6% were positive for TTG Ab, with 24.6% having celiac disease.
  - 1.0% were positive for 21-OH Ab, of whom one had Addison disease.

Diabetes Care 34:1211–1213, 2011

23



The prevalence of associated endocrine (black) and non-endocrine (light grey) autoimmune diseases in patients with type 1 diabetes + autoimmune diseases

World J Diabetes. 2020 Nov 15; 11(11): 527–539.

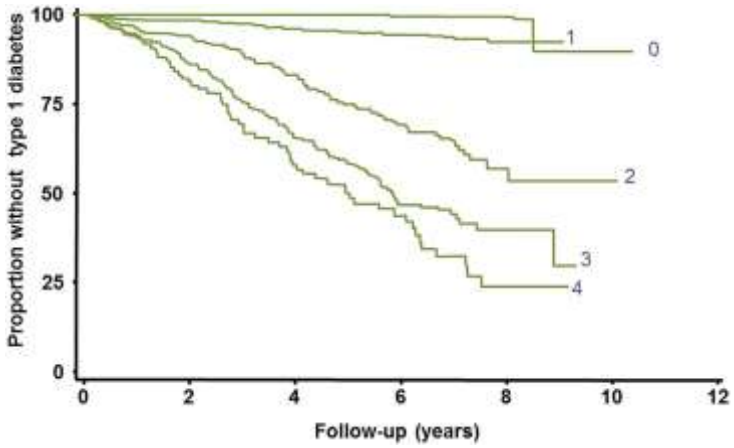
24

Antibodies Associated with Type 1 Diabetes

- Anti-GAD_{65} (glutamic acid decarboxylase)
- Anti-IA-2 Ab (or ICA 512)
- Anti-islet cell (ICA)
- Anti-insulin Ab
- Zn-T8 antibodies

25

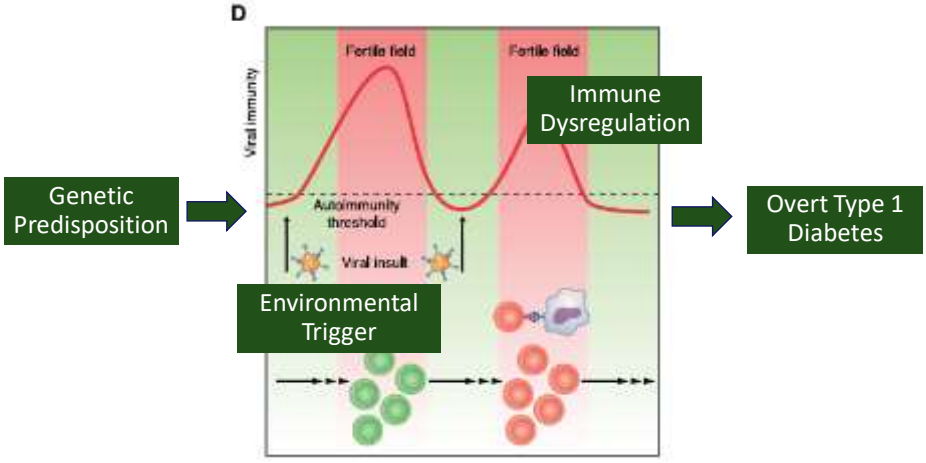
More Antibodies = Greater Risk of T1D



Diabetes Care. 2015;38(10):1964-1974. doi:10.2337/dc15-1419

26

The Pathogenesis of Type 1 Diabetes



van Belle TL, et al. *Physiol Rev.* 2011;91:79-118.

27

The Stages of Type 1 Diabetes

28

The Stages of Type 1 Diabetes

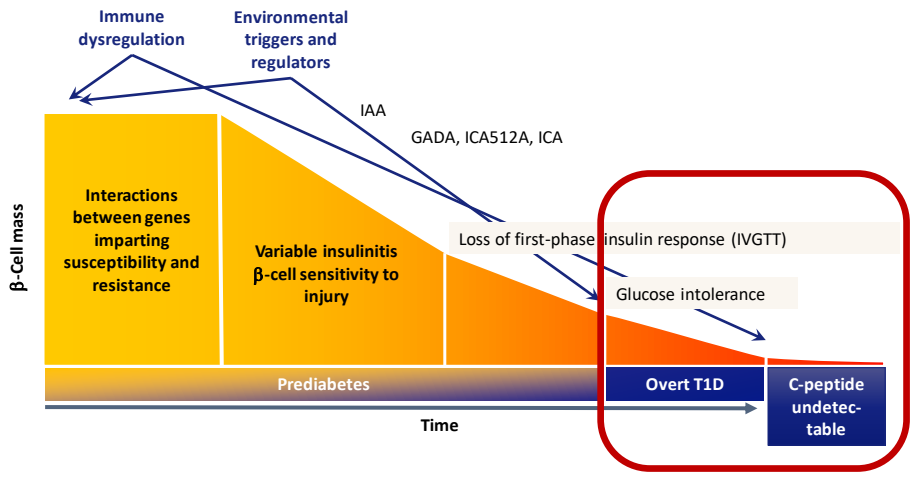
- More than 300,000 people in the United States are in the presymptomatic stages of type 1 diabetes.
- Beta-cell destruction begins months to years before the onset of T1D symptoms
- Most who are at increased risk for developing overt type 1 diabetes are not aware.[1,2]
- 30-50% of children with new onset T1D present with DKA

Early detection allows prevention of diabetic ketoacidosis (DKA) at onset of diabetes and allows patients and their families to participate in interventions and clinical trials that may delay or prevent disease.

From: https://connectedbyt1d.com/t1d-risk

29

The Progression of Type 1 Diabetes Takes Place over Months and Years



Atkinson MA. *Diabetes*. 2005;54:1253-1263. Adapted from Atkinson MA, Eisenbarth GS. *Lancet*. 2001;358:221-229.

30

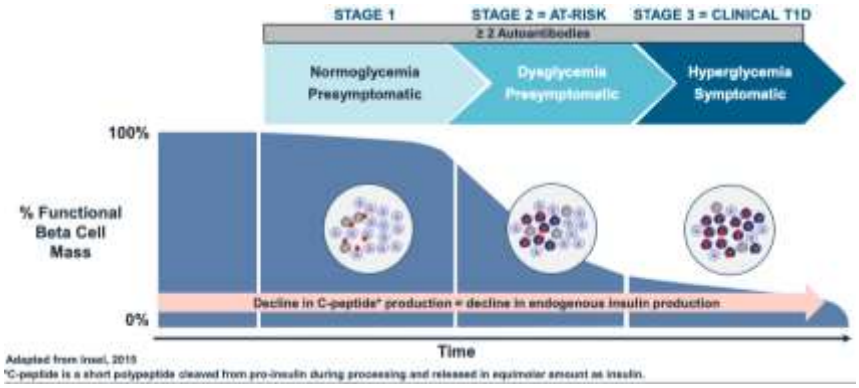
30

In 2015, the American Diabetes Association, JDRF, and Endocrine Society released T1D STAGING GUIDELINES based on islet autoantibody status and glycemic status in an effort to identify pre-symptomatic disease.

Diabetes Care. 2015;38(10):1964-1974. doi:10.2337/dc15-1419

31

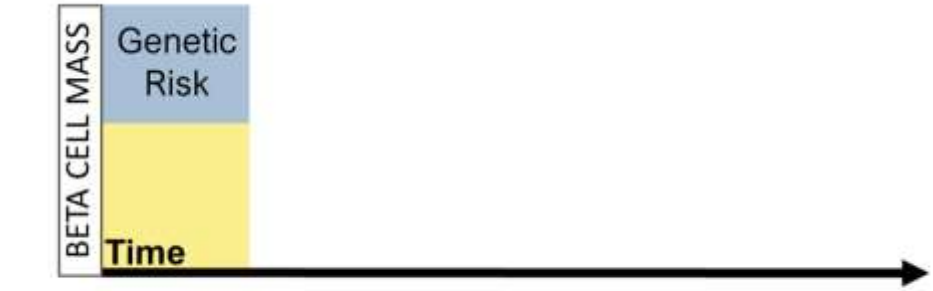
Type 1 Diabetes: The Three Stages of Progression



From: https://www.fda.gov/media/149543/download

32

Type 1 Diabetes:
The Three Stages of Progression

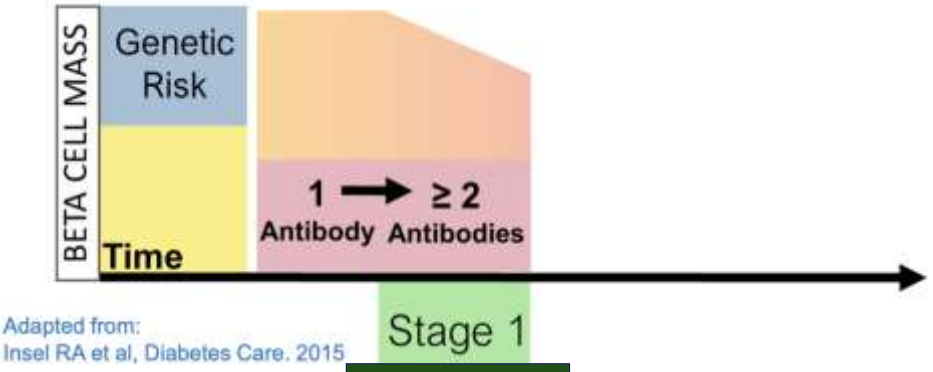


Adapted from:
Insel RA et al, Diabetes Care. 2015

From: https://www.fda.gov/media/149543/download

33

Type 1 Diabetes:
The Three Stages of Progression



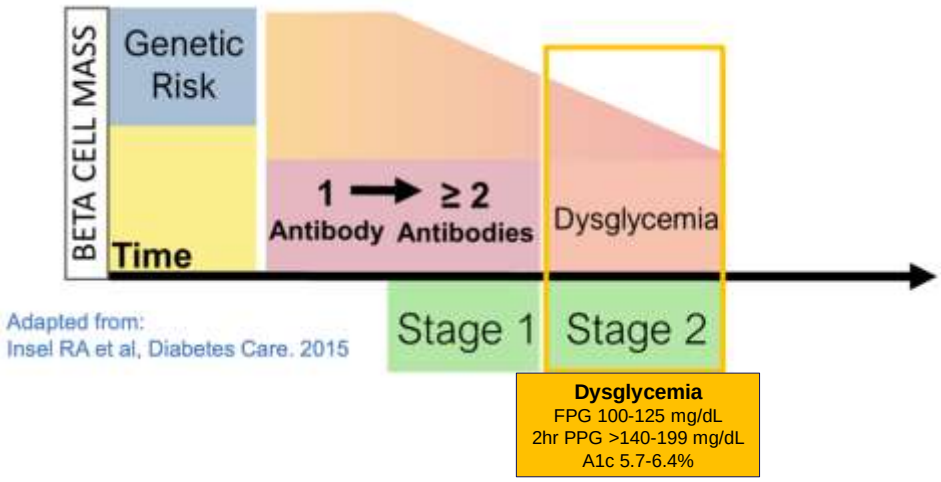
Adapted from:
Insel RA et al, Diabetes Care. 2015

Normoglycemia
FPG <100 mg/dL
2hr PPG <140 mg/dL
A1c <5.7%

From: https://www.fda.gov/media/149543/download

34

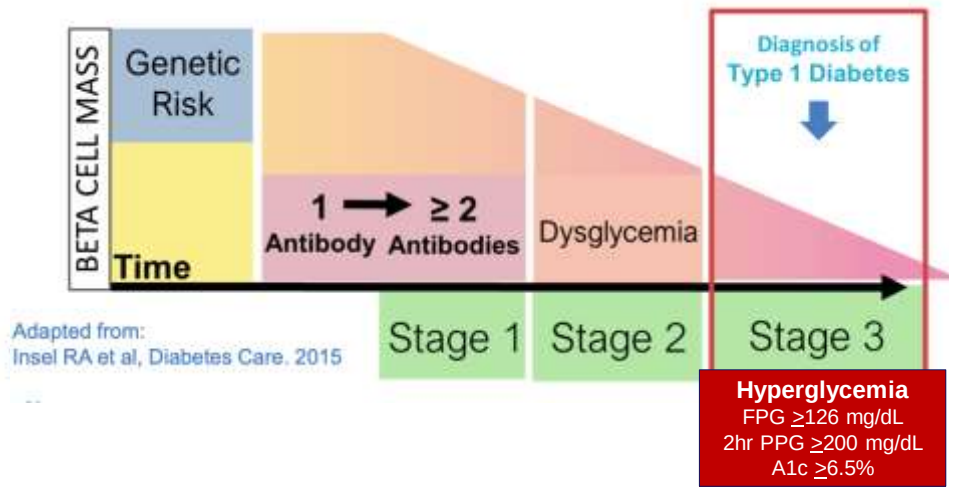
Type 1 Diabetes: The Three Stages of Progression



From: https://www.fda.gov/media/149543/download

35

Type 1 Diabetes: The Three Stages of Progression



From: https://www.fda.gov/media/149543/download

36

Most Individuals with ≥ 2 Autoantibodies Eventually Progress to Stage 3 Clinical T1D

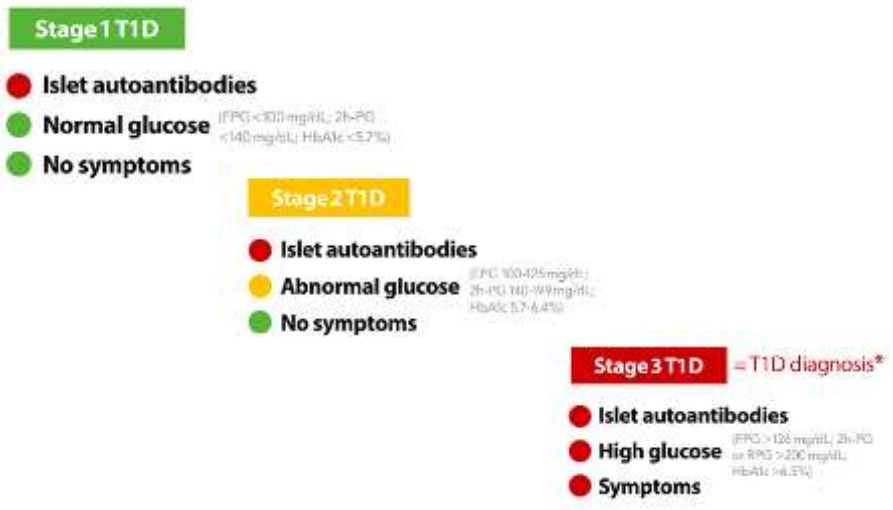
- Lifetime risk of progression[1] to Stage 3 nearly 100% for Stages 1 and 2
- 5-year risk of progression to Stage 3 clinical disease[1]
  - Stage 1: 44%
  - Stage 2: 75%
- Disease progression similar regardless of familial relationship or general population[2]

1. Insel, 2015; 2. Ziegler, 2013

From: https://www.fda.gov/media/149543/download

37

Stages of Type 1 Diabetes



From: https://www.asktheexperts.org/for-providers

38

Screening for Risk of Type 1 Diabetes

39

Why Screen Those at Risk?

- **Diabetic ketoacidosis (DKA) is a serious event, but screening can identify patients who may be at increased risk**[3]
  - *Screening for islet autoantibodies has been shown to reduce the incidence of DKA at diagnosis of Stage 3 T1D by ≥50%.*[1,2]
- **Patients who were screened experienced an ~8x lower likelihood of DKA at clinical onset of Stage 3 T1D.**[4]
  - ~30% to ~50% of children in the United States experience DKA at the onset of Stage 3 T1D[5]
  - Children with moderate or severe DKA were less likely to experience a "honeymoon phase" than children without DKA at diagnosis[6]

From: https://connectedbyt1d.com/proactive-screening

40

Risk of Developing Stage 3 Type 1 Diabetes

From: https://connectedbyt1d.com/stages-of-t1d

41

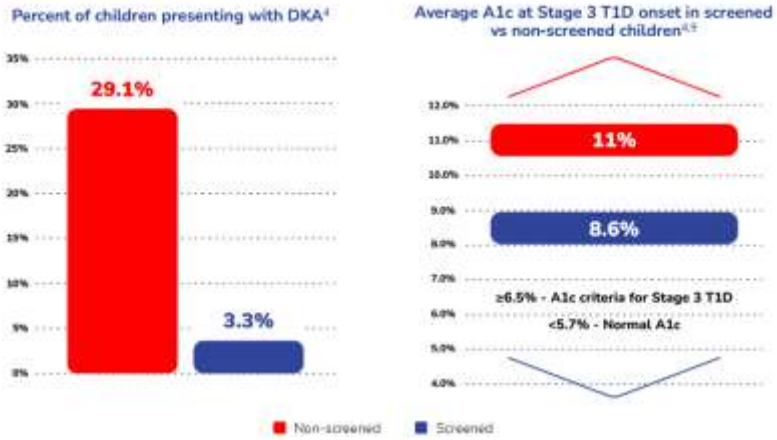
Metabolic and physical consequences of DKA at onset

- *DKA at onset may cause a "metabolic scar" in patients, which can lead to worse metabolic control in the short and longer term.*[3]
  - Lower residual beta-cell function[3,6]
  - Higher HbA1c for at least 15 years[7]
  - Rare neurological trauma such as cerebral edema[8]

From: https://connectedbyt1d.com/proactive-screening

42

Early identification can improve outcomes at onset of Stage 3 T1D

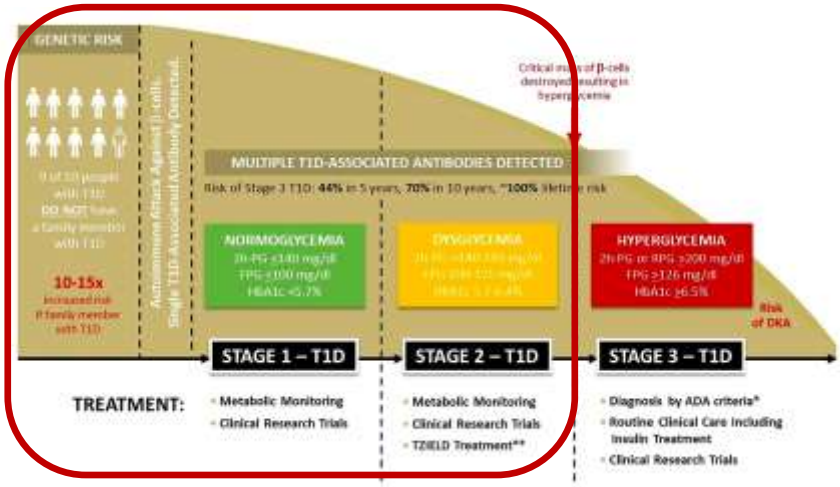


Screening can help identify patients who might benefit from enhanced clinical vigilance and education.

From: https://connectedbyt1d.com/proactive-screening

43

Screening for Risk of Type 1 Diabetes



From: https://www.asktheexperts.org/for-providers

44

Screening Laboratories and Programs

	Where do you LIVE to participate?	What AGES can be screened?	Screen for T1D	Screen for CELIAC	Requires ORDER from HCP
Research Based Screening Programs					
ASK	United States	1 to <18 yrs	✓	✓	No
CASCADE	Washington State	Newborn to 7 yrs	✓	✓	No
PLEDGE	South Dakota (must be Sanford Health patient)	Newborn to <6 yrs and 9 to <17yrs	✓	✓	No
TrialNet	United States	2.5 to 45 yrs and parent, brother/sister, or child with T1D — OR — 2.5 to 20 yrs with aunt/uncle, cousin, grandparent, niece/nephew, or half-sibling with T1D	✓	⊗	No
Consumer Laboratory					
Enable Biosciences	United States (except NY and PA)	Over 1 yr	✓	⊗	No
Clinical Laboratory					
LabCorp	United States	ALL ages	✓	✓	Yes
Mayo Laboratories	United States	ALL ages	✓	✓	Yes
Quest	United States	ALL ages	✓	✓	Yes

From: https://www.asktheexperts.org/for-providers

45

Screening Result= Negative

•PERSONAL HISTORY of autoimmunity
and/or
•FAMILY HISTORY of autoimmune disease

CONSIDER REPEAT SCREENING ANNUALLY

•Repeat at ANY age if symptoms of type 1 diabetes appear (also check glucose level and HbA1c)

•NO PERSONAL HISTORY of autoimmunity
and
•NO FAMILY HISTORY of autoimmune disease

For AGE <15yrs:

•Repeat at ANY age if symptoms of type 1 diabetes appear (also check glucose level and HbA1c)

From: https://www.asktheexperts.org/for-providers

46

Screening Result= Positive

Evaluate Glycemic Status

- Upon receiving a positive screening result- check blood glucose and A1C to determine glycemic status and rule out a diagnosis of overt diabetes.

Normoglycemia	Dysglycemia	Hyperglycemia
FPG <100 mg/dL	FPG 100-125 mg/dL	FPG ≥126 mg/dL
2hr PPG <140 mg/dL	2hr PPG >140-199 mg/dL	2hr PPG ≥200 mg/dL
A1c <5.7%	A1c 5.7-6.4%	A1c ≥6.5%

Confirm Positive Result

- All four T1D associated antibodies must be measured: GAD-65 antibody, IA-2 antibody, insulin antibody, ZnT8 antibody

From: https://www.asktheexperts.org/for-providers

47

Screening Result= Positive

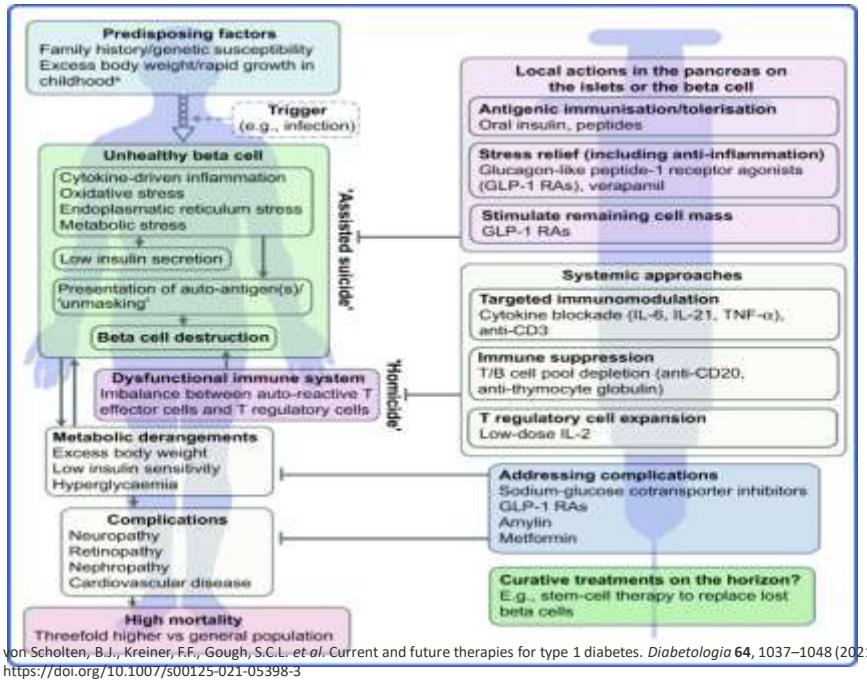
If your patient screened POSITIVE, and is confirmed POSITIVE, they must be monitored for progression to type 1 diabetes.

From: https://www.asktheexperts.org/for-providers

48

Past Attempts at Prevention of Type 1 Diabetes

49



von Scholten, B.J., Kreiner, F.F., Gough, S.C.L. *et al*. Current and future therapies for type 1 diabetes. *Diabetologia* **64**, 1037–1048 (2021). https://doi.org/10.1007/s00125-021-05398-3

50

Past Attempts to Delay or Prevent Type 1 Diabetes

Azathioprine — immunosuppressive drug that inhibits or prevents T cell responses to antigens.

In one randomized, double-blind study of 46 patients treated with azathioprine and glucocorticoids, insulin could be discontinued in 10 of 20 treated patients as compared with 2 of 20 patients in the placebo group

Endogenous insulin secretion (measured as the plasma C-peptide response to a liquid meal) also improved. However, only three treated patients remained in remission at one year.

Equally discouraging results were noted in a second study

From: Irl Hirsh, Up to Date. Prevention of type 1 diabetes mellitus

51

Past Attempts to Delay or Prevent Type 1 Diabetes

Mycophenolate mofetil — inhibits proliferation of both T- and B-lymphocytes.

In a multicenter, randomized trial, 126 patients with type 1 diabetes for less than three months were randomly assigned to MMF, MMF plus daclizumab (an anti-interleukin [IL]-2 receptor monoclonal antibody that selectively binds the IL-2 receptor, inhibiting IL-2-mediated T-lymphocyte proliferation), or placebo

After two years, there was no significant difference in the mean AUC for C-peptide levels during a mixed-meal tolerance test.

From: Irl Hirsh, Up to Date. Prevention of type 1 diabetes mellitus

52

Past Attempts to Delay or Prevent Type 1 Diabetes

Cyclosporine — Large-scale trials in patients with recently diagnosed type 1 diabetes in Canada and France showed that remissions were twice as common in the cyclosporine-treated patients as compared with placebo.

Although the remissions also lasted longer, almost all patients required insulin again within three years.

Bacillus Calmette-Guerin (BCG) — A trial randomly assigned 72 patients with new-onset (less than four weeks) type 1 diabetes to therapy with nicotinamide alone or in combination with BCG

The number of patients in remission in each group was three at three months and none at 12 months.

From: Irl Hirsh, Up to Date. Prevention of type 1 diabetes mellitus

53

Past Attempts to Delay or Prevent Type 1 Diabetes

TNF-alpha inhibitors — In a 24-week trial of etanercept versus placebo in 18 patients with newly diagnosed type 1 diabetes, patients assigned to etanercept had lower A1C values (5.9 versus 7.0 percent) and greater increases in C-peptide AUC (39 percent increase versus 20 percent decrease)

Larger trials are required to assess the benefits and risks of etanercept for the prevention of type 1 diabetes.

Interferon alfa — In a 12-month trial of oral human recombinant interferon alfa-2a (IF-a) versus placebo in 128 patients with newly diagnosed type 1 diabetes, patients randomly assigned to IF-a (5000 units daily) had a smaller percentage loss of mixed-meal stimulated C-peptide (28 versus 56 percent), but, there were no differences in A1C or insulin requirements.

From: Irl Hirsh, Up to Date. Prevention of type 1 diabetes mellitus

54

Past Attempts to Delay or Prevent Type 1 Diabetes

Glucocorticoids— No lasting effect

DiaPep277 — c-peptide was preserved at 10 months, long term effect unknown

GAD65 immunotherapy— No difference

Insulin— Nasal, oral, or SQ insulin did not delay or prevent T1D in high risk individuals (studies are on-going with higher dose)

Nicotinamide— ineffective

Vitamin D — unclear (there was an increased risk of lower fasting C-peptide with Vit D in one study)

Avoidance of Cows Milk— No difference

Gluten free diet— No effect

Omega 3 — Prospective trial is on going

From: Irl Hirsh, Up to Date. Prevention of type 1 diabetes mellitus

55

Past Attempts to Delay or Prevent Type 1 Diabetes

Anti-CD3 antibodies — Treatment of mice with an anti-CD3 monoclonal antibody (OKT3) reverses diabetes in nonobese diabetic (NOD) mice (a model in which spontaneous autoimmunity and pancreatic islet destruction occur)

However, OKT3 use is problematic in humans because of significant cytokine-mediated TNF-alpha related side effects.

Humanized monoclonal antibodies have been developed, which appear to have fewer major adverse effects (fever, headache, hypotension).

Anti-CD3 antibodies have been successfully used for the treatment of acute renal allograft rejection and psoriatic arthritis

From: Irl Hirsh, Up to Date. Prevention of type 1 diabetes mellitus

56

Past Attempts to Delay or Prevent Type 1 Diabetes

- Otelixizumab — anti-CD3 ab- multicenter trial (n=80) with new-onset T1D who were randomly assigned to otelixizumab for six consecutive days or placebo:
  - At 6, 12, and 18 months, residual beta-cell function, was better maintained in the anti-CD3 antibody group.
  - Insulin dose requirements increased in the placebo but not the treatment group.
  - In the subgroup of patients with initial residual beta-cell function at or above the 50th percentile, mean insulin dose at 18 months was lower in the treatment group
  - Treatment was associated with significant but transient side effects, including fever after the start of infusions and rash and acute mononucleosis-like syndrome after the end of treatment.
  - In a follow-up report on 64 patients followed for a mean of 48 months, there was a delay in the rise in insulin requirements

From: Irl Hirsh, Up to Date. Prevention of type 1 diabetes mellitus

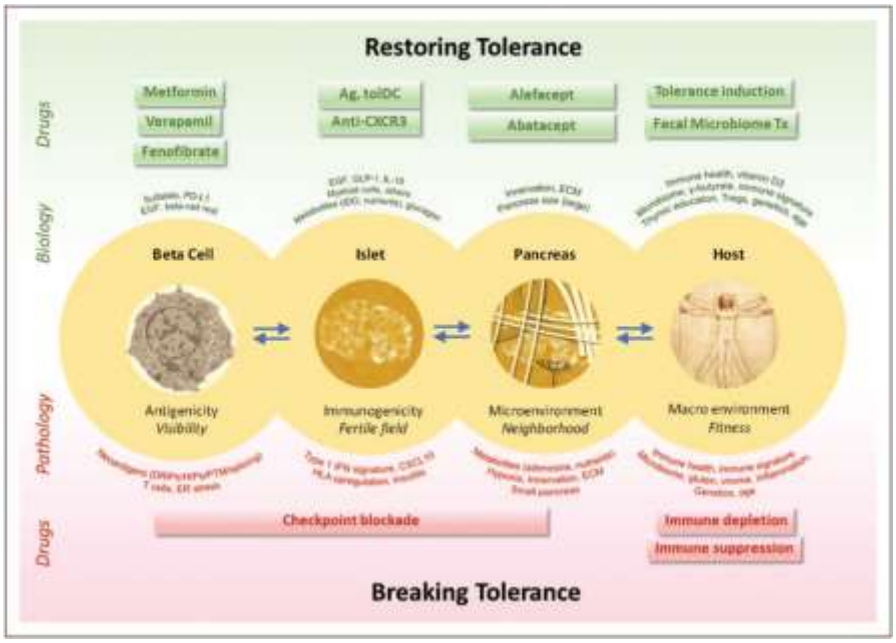
57

Past Attempts to Delay or Prevent Type 1 Diabetes

- Teplizumab — A monoclonal antibody, termed hOKT3gl (Ala-Ala) (teplizumab)
- Teplizumab has been studied in patients with recently diagnosed type 1 diabetes as well as in individuals at high risk for developing type 1 diabetes.
- In individuals at high risk, teplizumab has been shown to delay progression to stage 3 (symptomatic) type 1 diabetes.
- In patients with recently diagnosed type 1 diabetes, trial results have been inconsistent.
- Adverse effects include transient lymphopenia, rash, anemia, and fever.

From: Irl Hirsh, Up to Date. Prevention of type 1 diabetes mellitus

58



Erdem, N et al Breaking and restoring immune tolerance to pancreatic beta-cells in type 1 diabetes. Current Opinion in Endocrinology & Diabetes and Obesity 28(4):p 397-403,

59

Teplizumab

A New Treatment Option to Delay the Onset of Overt Type 1 Diabetes

60

A New Treatment Option to Delay Onset of Clinical Type 1 Diabetes

- On November 17, 2022, the FDA approved TZIELD (teplizumab).
- TZIELD is the first FDA-approved treatment for early diabetes and has the potential to delay the onset of clinical type 1 diabetes (T1D).
- It is approved for adults and pediatric patients aged 8 years and older with Stage 2 T1D.
- Stage 2 T1D definition:
  - 2 or more T1D-associated autoantibodies (GAD, IAA, IA-2, ICA512, and/or ZnT8A)
  - Dysglycemia.

61

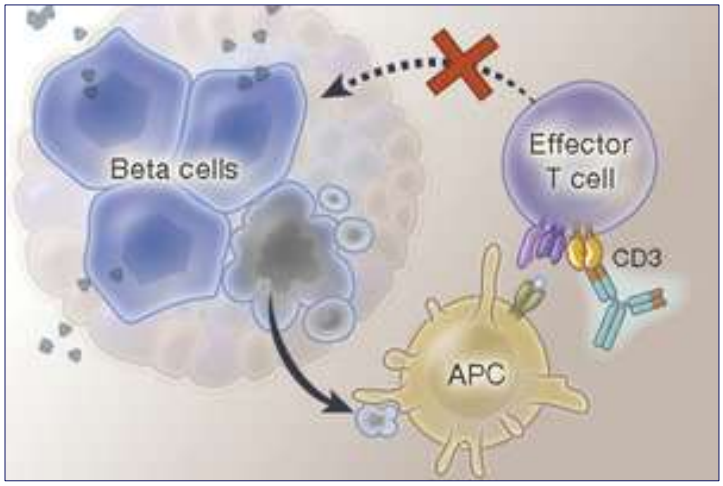
Teplizumab

- A *descendent* of **OKT3 (muromonab)**
  - The first FDA approved monoclonal antibody
  - OKT3 is associated with cytokine release syndrome and immunogenicity
- Teplizumab is a humanized version of OKT3
  - Modified to be less immunogenic
  - Initially intended to be a more tolerable treatment for renal transplant rejection
- Mechanistic rationale for use in T1D:
  - Interferes with T-cell mediated autoimmune destruction of beta cells

From: https://www.fda.gov/media/149543/download

62

Teplizumab



N Engl J Med 2019; 381:603-613

63

Teplizumab

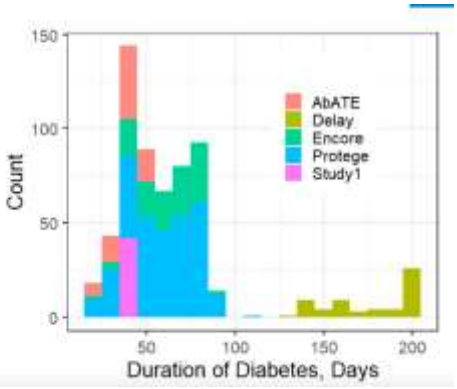
- 8 studies in non diabetes disease

From: https://www.fda.gov/media/149543/download

64

Studies Prior to TN-10
Duration of Type 1 DM at Baseline

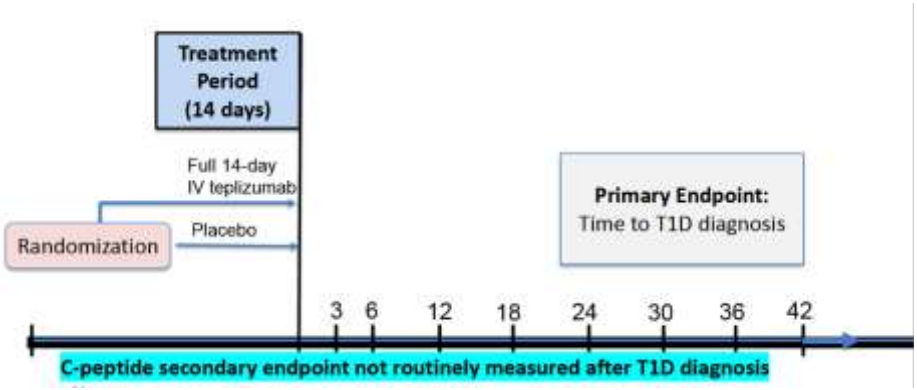
Study	*T1D Duration*
AbATE	≤ 8 weeks
Delay	4 -12 months
Encore	≤ 12 weeks
Protege	≤ 12 weeks
Study 1	≤ 6 weeks



From: https://www.fda.gov/media/149543/download

65

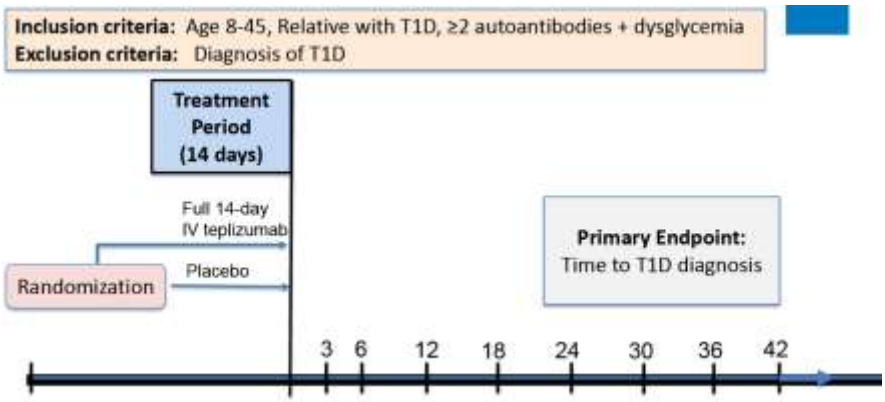
TN-10 Study Design



From: https://www.fda.gov/media/149543/download

66

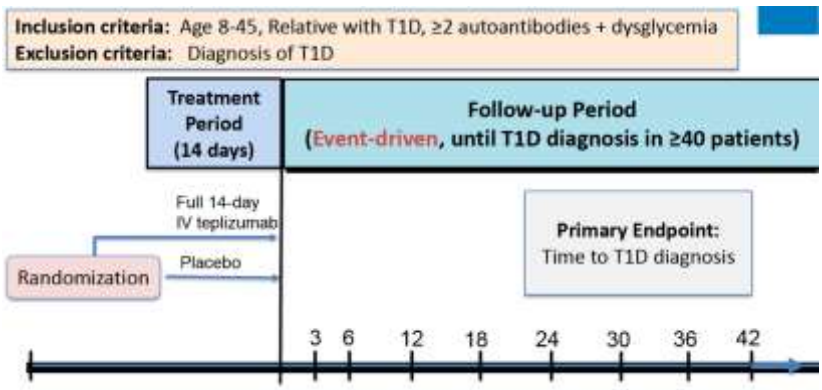
TN-10 Study Design



From: https://www.fda.gov/media/149543/download

67

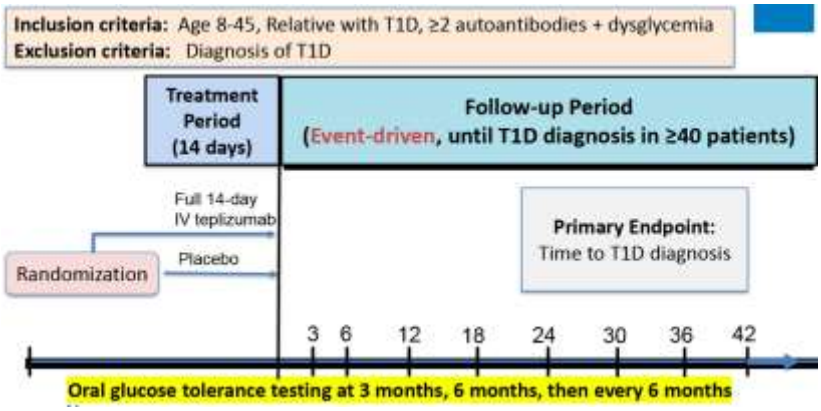
TN-10 Study Design



From: https://www.fda.gov/media/149543/download

68

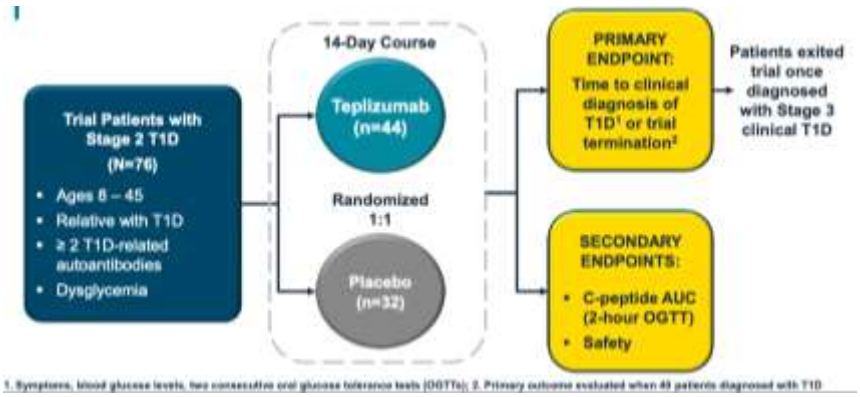
TN-10 Study Design



From: https://www.fda.gov/media/149543/download

69

TN-10 Study Design



From: https://www.fda.gov/media/149543/download

70

TN-10
Baseline Demographics

Characteristic	Teplizumab N=44	Placebo N=32
Age (years), mean (SD)	19 (11.9)	18 (11.1)
Median (min, max)	14 (8.5, 49.5)	13 (8.6, 45.0)
< 18 years	66%	81%
Male	57%	53%
Race		
White	100%	94%
Asian	0%	3%
Multiple	0%	3%
BMI (kg/m^2), mean (SD)	22.0 (6.4)	22.1 (4.4)
Median (min, max)	20.0 (14.7, 43.7)	21.6 (16.0, 34.6)

From: https://www.fda.gov/media/149543/download

71

TN-10
Baseline Metabolic Characteristics

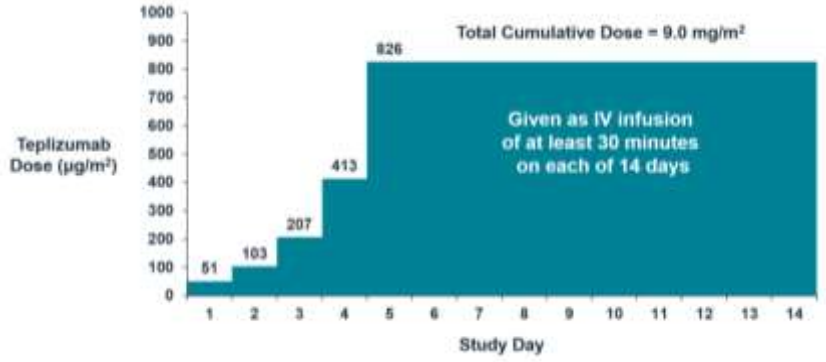
Clinical Characteristics	Teplizumab N=44	Placebo N=32	Normal Range
Fasting Glucose (mg/dL), median (min, max)*	95.0 (79, 113)	96.5 (45, 120)	< 100
C-peptide AUC in OGTT (nmol/L), median (SD)	1.8 (0.6, 4.4)	1.7 (0.7, 3.8)	~ 1.2 – 3.3
HbA1c (%), median (SD)	5.2 (4.6, 6.1)	5.3 (4.3, 5.6)	< 5.7

*Derived from time 0 of baseline OGTTs

From: https://www.fda.gov/media/149543/download

72

TN-10:
Single 14-day Course of IV Treatment



From: https://www.fda.gov/media/149543/download

73

Criteria for Diagnosis of Diabetes in TN-10

- Type 1 diabetes was diagnosed by the following criteria:
  - 2-hour plasma glucose ≥200 mg/dL on oral glucose tolerance testing
  - casual plasma glucose >200 mg/dL plus symptoms of diabetes (polyuria/polydipsia/weight loss)
  - fasting plasma glucose ≥ 126 mg/dL

  * criteria had to be confirmed **on two occasions** at least 1 day apart
- In addition, the presence of unequivocal hyperglycemia with acute metabolic decompensation (diabetic ketoacidosis) was also considered diagnostic of type 1 diabetes

From: https://www.fda.gov/media/149543/download

74

Safety- Disposition

In TN-10, there were similar rates of study completion* between groups

Teplizumab vs. Placebo

(93%) vs. (91%)

*Completion: met primary endpoint, or follow-up ongoing at cutoff date

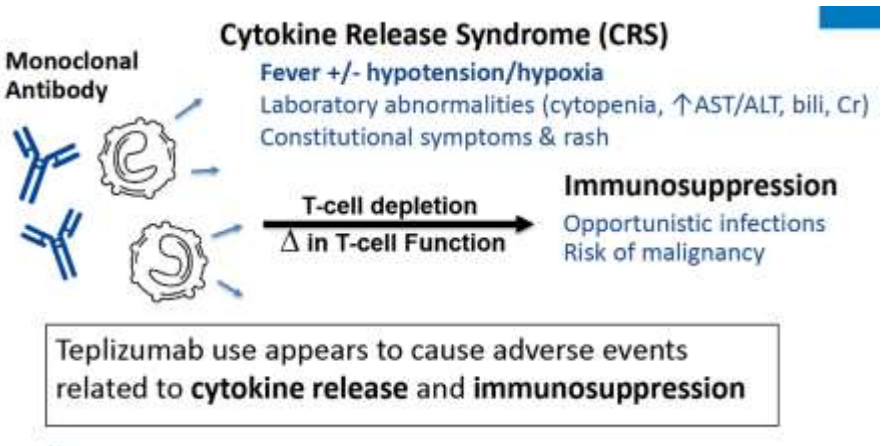
In the pool of all studies except TN-10, there was a high percentage of completers in each group at one-year

	Teplizumab	Control
Completers:	89%	93%

From: https://www.fda.gov/media/149543/download

75

Adverse Events of Special Interest



From: https://www.fda.gov/media/149543/download

76

Serious Adverse Events (SAE)

SAEs # in all studies, first and second cycle

SAE	Teplizumab N=773 n (%)	Control N=245 n (%)	Risk Difference (%)	Relative Risk	Relative Risk 95% CI
Diabetic ketoacidosis	18 (2.3)	1 (0.4)	1.9	5.75	(0.8, 42.5)
Infection*	26 (3.4)	5 (2.0)	1.4	1.70	(0.6, 4.1)
Hypoglycaemic seizure	6 (0.8)	0 (0.0)	0.8	-	-
Cytokine release syndrome	5 (0.6)	0 (0.0)	0.6	-	-
Hypoglycemia*	13 (1.7)	3 (1.2)	0.5	1.42	(0.4, 4.9)
Hepatic injury*	4 (0.5)	0 (0.0)	0.5	-	-

From: https://www.fda.gov/media/149543/download

77

Adverse Events

Adverse events reported in at least 10% of teplizumab patients and > control, all studies, first cycle

Adverse Event	Teplizumab N=773 n (%)	Placebo N=245 n (%)	Risk Difference (%)	Relative Risk	Relative Risk 95% CI
Lymphopenia*	594 (76.8)	23 (9.4)	67.4	8.2	(5.5, 12.1)
Leukopenia*	635 (82.1)	59 (24.1)	58.0	3.4	(2.7, 4.3)
Rash*	344 (44.5)	22 (9.0)	35.5	4.9	(3.3, 7.5)
Transaminases elevated*	189 (24.5)	26 (10.6)	13.9	2.3	(1.6, 3.4)
Neutropenia	185 (23.9)	29 (11.8)	12.1	2.0	(1.4, 2.9)
Pruritus*	117 (15.1)	13 (5.3)	9.8	2.9	(1.7, 5.1)
Thrombocytopenia*	102 (13.2)	11 (4.5)	8.7	2.9	(1.6, 5.3)
Pyrexia	120 (15.5)	17 (6.9)	8.6	2.3	(1.4, 3.6)
Blood bicarbonate decreased	116 (15.0)	16 (6.5)	8.5	2.3	(1.4, 3.8)
Nausea*	106 (13.7)	15 (6.1)	7.6	2.3	(1.3, 3.7)
Anemia*	211 (27.3)	52 (21.2)	6.1	1.3	(1, 1.7)
Hypocalcemia*	143 (18.5)	31 (12.7)	5.8	1.5	(1, 2.2)
Headache*	136 (17.6)	35 (14.3)	3.3	1.2	(0.9, 1.8)
Hyponatremia*	158 (20.4)	43 (17.6)	2.8	1.2	(0.9, 1.6)
Hypocalcemia	88 (11.4)	23 (9.4)	2.0	1.2	(0.8, 1.9)

From: https://www.fda.gov/media/149543/download

78

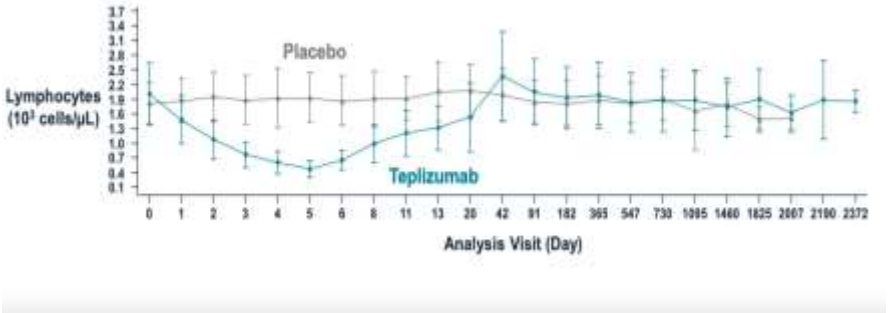
Most Common Adverse Events >10%

Preferred Term	Teplizumab N=44		Placebo N=32	
	n	%	n	%
Patients with ≥ 1 AE	43	98%	22	69%
Lymphopenia	32	73%	2	6%
Leukopenia	9	21%	0	0
Nasopharyngitis	7	16%	2	6%
Rash pruritic	7	16%	0	0
Rash	6	14%	0	0
Headache	5	11%	3	9%

From: https://www.fda.gov/media/149543/download

79

Transient Lymphopenia During Treatment Course



From: https://www.fda.gov/media/149543/download

80

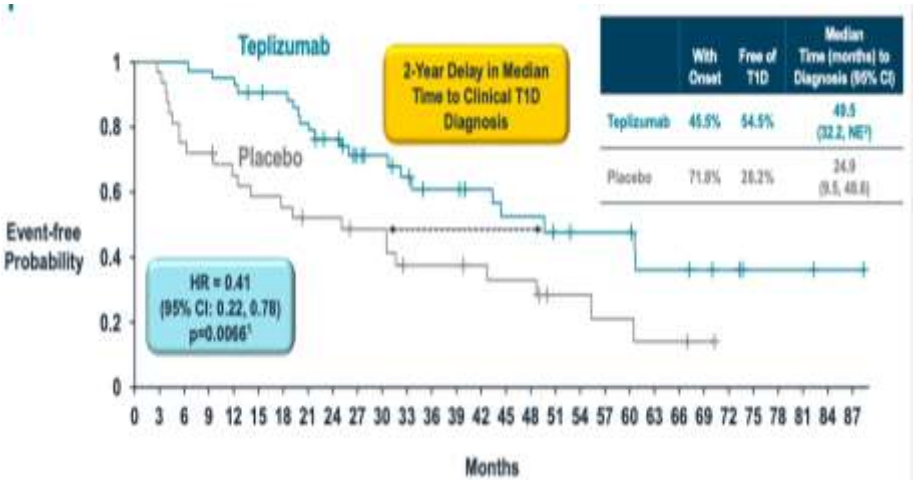
TN-10: Study Results

- In Stage 2 T1D or at-risk individuals, single 14-day course of teplizumab
  - Significantly delayed median time to clinical T1D by minimum of 2 years vs placebo
  - Had numerically more patients free of clinical T1D beyond 5 years vs placebo
  - C-peptide results support effect on preserving beta cell function
- Meta-analyses of 5 additional randomized-controlled trials with 1 or 2 courses of teplizumab in patients with Stage 3 T1D confirm effect at 1 and 2 years

From: https://www.fda.gov/media/149543/download

81

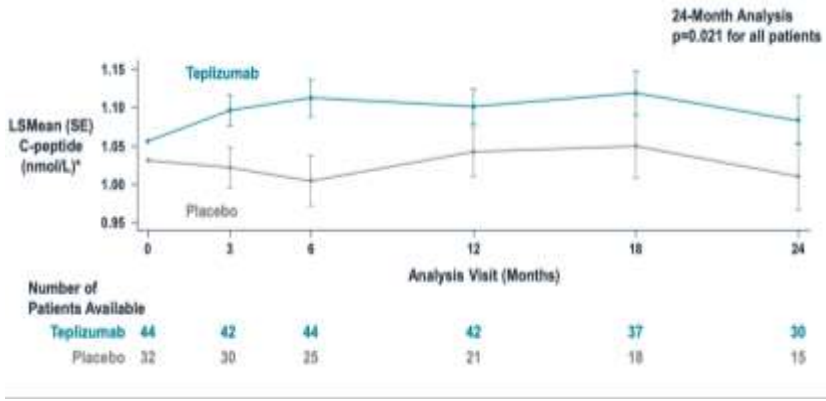
TN-10: Primary Endpoint



From: https://www.fda.gov/media/149543/download

82

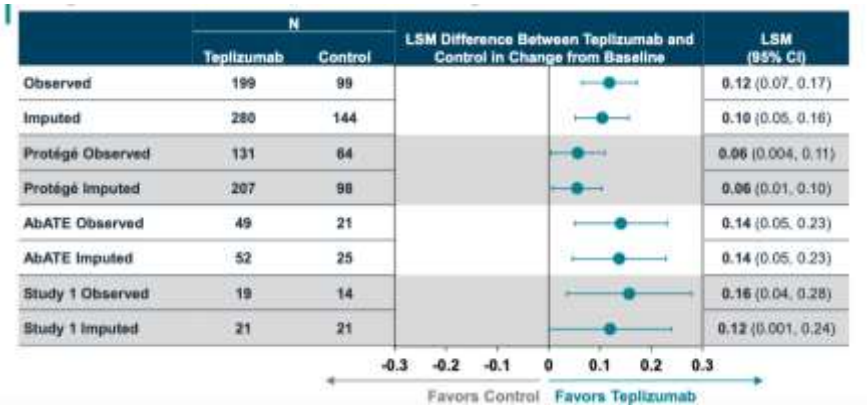
TN-10: C-Peptide



From: https://www.fda.gov/media/149543/download

83

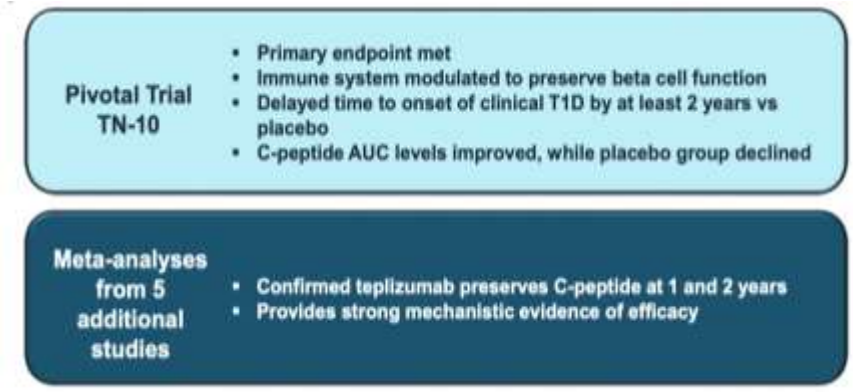
TN-10: C-Peptide



From: https://www.fda.gov/media/149543/download

84

Teplizumab Delayed Clinical Onset of T1D in Patients with Stage 2 Disease



From: https://www.fda.gov/media/149543/download

85

Teplizumab: Safety Profile

- TN-10 Safety
  - No new safety signals beyond those observed in earlier Stage 3 studies
- Pooled Safety
  - Nearly 800 patients exposed to teplizumab representing ~ 1500 patient-years of follow-up
  - Most AEs related to teplizumab mechanism-based, predictable, transient, and manageable

From: https://www.fda.gov/media/149543/download

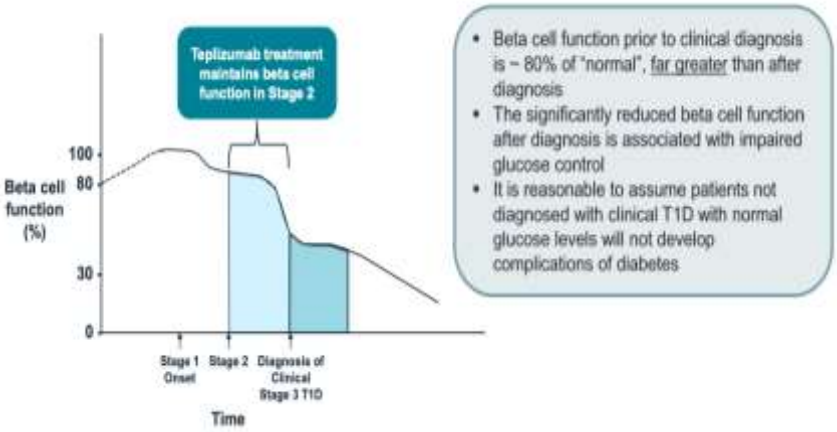
86

TN-10: First Study to Show that a Treatment can Modify Disease Progression of T1D

From: https://www.fda.gov/media/149543/download

87

Teplizumab Treatment Prevents Decline in Beta Cell Function



From: https://www.fda.gov/media/149543/download

88

Teplizumab: Potential Adverse Effects are Transient and Manageable

- Well-understood AE profile
  - Most common AEs predictable and self-limited (lymphopenia and rash)
- If CRS occurs, it is mild or moderate and transient
  - Treated with NSAIDs, antihistamines, and/or acetaminophen without steroids
- Long-term sequelae seen with other immunologic therapies do not occur
- To date, no increase in serious infections or malignancies
- 7-year follow-up in newly diagnosed patients shows no long-term safety concerns[1]

From: https://www.fda.gov/media/149543/download

89

Teplizumab: Benefits Outweigh Risks for Patients Facing Life Long Insulin Dependent Disease

- Freedom from clinical T1D has significant benefit
- Teplizumab given as a brief treatment is safe and has potential long-term benefits
- Beyond 5 years, 8/44 (18%) teplizumab-treated Stage 2 patients do not have clinical diabetes vs 2/32 (6%) in placebo group

Teplizumab is the first drug to demonstrate preservation of beta cell function leading to delay in onset of and, potentially in some patients, the prevention of clinical T1D

From: https://www.fda.gov/media/149543/download

90

Tzield (teplizumab)
Prescribing Information

91

Tzield (Teplizumab) Indications and Usage

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.

From: https://tzieldhcp.com

92

Tzield (Teplizumab) Dosage and Administration

- Confirm Stage 2 T1D by documenting at least two positive pancreatic islet autoantibodies in those who have dysglycemia without overt hyperglycemia using an oral glucose tolerance test (OGTT) or alternative method if appropriate and OGTT is not available
- In patients who meet criteria for a diagnosis of Stage 2 type 1 diabetes, ensure the clinical history of the patient does not suggest type 2 diabetes

From: https://tzieldhcp.com

93

Tzield (Teplizumab) Dosage and Administration

- Prior to initiating TZIELD, obtain a complete blood count and liver enzyme tests.
- Use of TZIELD is not recommended in patients with certain laboratory abnormalities:
  - Lymphocyte count less than 1,000 lymphocytes/mcL
  - Hemoglobin less than 10 g/dL
  - Platelet count less than 150,000 platelets/mcL
  - Absolute neutrophil count less than 1,500 neutrophils/mcL
  - Elevated ALT or AST greater than 2 times the upper limit of normal (ULN) or bilirubin greater than 1.5 times ULN
  - Laboratory or clinical evidence of acute infection with Epstein-Barr virus (EBV) or cytomegalovirus (CMV)
  - Active serious infection or chronic active infection other than localized skin infections

From: https://tzieldhcp.com

94

Tzield (Teplizumab) Dosage and Administration

- Administer all age-appropriate vaccinations prior to starting TZIELD
  - Administer live-attenuated (live) vaccines at least 8 weeks prior to treatment.
  - Administer inactivated (killed) vaccines or mRNA vaccines at least 2 weeks prior to treatment.

From: https://tzieldhcp.com

95

Tzield (Teplizumab) Dosage and Administration

Before each TZIELD dose for at least the first 5 days of the 14-day treatment course, premedicate with:

1. Nonsteroidal anti-inflammatory drug (NSAID) or acetaminophen, and/or
2. Antihistamine, and/or
3. Antiemetic

From: https://tzieldhcp.com

96

Tzield (Teplizumab)
Recommended Dosage and Administration

- Administer TZIELD by intravenous infusion (over a minimum of 30 minutes), using a body surface area-based dosing, once daily for 14 consecutive days as follows:
  - Day 1: 65 mcg/m2
  - Day 2: 125 mcg/m2
  - Day 3: 250 mcg/m2
  - Day 4: 500 mcg/m2
  - Days 5 through 14: 1,030 mcg/m2
- Do not administer two doses on the same day.

From: https://tzieldhcp.com

97

Tzield (Teplizumab)
Warnings and Precautions

- Cytokine Release Syndrome (CRS):
  - Premedicate and monitor liver enzymes
  - Discontinue in those that develop elevated ALT or AST more than 5 times the upper limit of normal
  - If severe CRS develops consider temporarily pausing dosing

From: https://tzieldhcp.com

98

Tzield (Teplizumab)
Warnings and Precautions

- Serious Infections: Use of TZIELD is not recommended in patients with active serious infection or chronic infection.
- Monitor for signs and symptoms of infection during and after TZIELD treatment.
- If a serious infection develops, discontinue TZIELD

From: https://tzieldhcp.com

99

Tzield (Teplizumab)
Warnings and Precautions

- Lymphopenia: Monitor white blood cell counts during the treatment period.
  - If prolonged severe lymphopenia (<500 cells per mcL lasting 1 week or longer) develops, discontinue TZIELD
- Hypersensitivity Reactions: If severe hypersensitivity reactions occur, discontinue TZIELD and treat promptly

From: https://tzieldhcp.com

100

Type 1 Diabetes: A New Breakthrough in Therapy

101

Conclusion

- The pathogenesis of type 1 diabetes requires a genetic predisposition, an environmental trigger, and the development of beta cell autoimmunity
- Even though most people experience the onset of type 1 diabetes with sudden onset of hyperglycemia and/or DKA, the progression of disease occurs in stages slowly over months and years.
- The more beta cell antibodies one has, the greater the likelihood of developing overt type 1 diabetes in the future (and sooner)
- Screening people at risk for T1D helps identify those who may benefit from enhanced clinical vigilance and education- and possibly from intervention with teplizumab
- Teplizumab is a new treatment indicated to delay the onset of Stage 3 type 1 diabetes in adults and children aged 8 years and older with Stage 2 T1D

102

Questions, Answers, and Unknowns

- What will be the insurance coverage issues and other barriers?
- What is the cost of treatment?
  - $13,850 a vial
  - Full course (estimated) = $193,900*
- Will beta cell antibody screening of those at risk be covered by insurance?
  - Estimated cost of testing all four antibodies = $1,189**
- What about wider screening of the general population?
  - Most people who develop T1D do not have family history
- Will there be other interventions in the future to increase response and length of delay in onset of T1D? Or prevent T1D completely?

* Med Page Today https://www.medpagetoday.com/endocrinology/type1diabetes/101823
** *Clin Diabetes* 2019;37(1):90–92

103

Thank you!

104