Prediction and Prevention of Type 1 Diabetes. How far to go?

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ISLET-CELL ANTIBODIES IN DIABETES MELLITUS WITH AUTOIMMUNE POLYENDOCRINE DEFICIENCIES

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Summary Antibodies to pancreatic islet cells were found by immunofluorescence in the sera of 13 patients with multiendocrine deficiencies associated with organ-specific autoimmunity. 10 of these patients were diabetic. The antibodies were complement fixing and of IgG class; titres varied from 1 to 160 and were independent of insulin treatment. The presence of organ-specific pancreatic antibodies supports the hypothesis of an autoimmune form of diabetes mellitus put forward to explain the histological “insulitis” found in selected cases of this disease. This new marker allows the segregation of a homogeneous group of insulin-dependent diabetics who may well prove to have a different metabolic pattern from that in other forms of inherited diabetes mellitus.
Joslin Diabetes Center Triplets
Islet cell antibodies in first degree relatives of patients with T1D predict diabetes

Natural History of T1D

- GENETICALLY AT-RISK
- ENVIRONMENTAL TRIGGER/S
- ISLET ANTIBODY POSITIVE
- FIRST PHASE INSULIN RESPONSE IMPAIRED

TIME

BETA CELLS

- GENETIC PREDISPOSITION
- INSULITIS BETA-CELL DAMAGE
- PRE-DIABETES
- DIABETES
1980s – immunotherapy at diagnosis

- Azathioprine
- Cyclosporin
- Azathioprine + prednisolone

‘….too late, or discontinuation of therapy results in a relapse of diabetes’

….. ‘too toxic’
Identification of antigen targets

Glutamic Acid Decarboxylase

Insulin

IA2

ZnT8
Defining workshop standards

FIRST INTERNATIONAL GADAb WORKSHOP

A

Result

B

Result

C

Units

D

Units
Diabetes Autoantibody Standardization Program (DASP)

A Collaborative Effort of the Immunology of Diabetes Society (IDS)
And the
Centers for Disease Control and Prevention (CDC)

Proficiency Testing (PT)

Novel Assay Evaluation (NAE)
Preclinical diabetes studies: identify subjects at risk and prevent T1D

Melbourne Pre-diabetes Family Study
- ~4000 first-degree relatives tested
- ~150 antibody-positive relatives
- ~60 followed with antibody, metabolic and cell-mediated immunity tests to clinical diabetes
The Melbourne Pre-Diabetes Study: prediction of type 1 diabetes mellitus using antibody and metabolic testing

Peter G Colman, Peter McNair, Heather Margetts, Robert S Schmidli, George A Werther, Frank P Alford, Glenn M Ward, Brian D Tait, Margo C Honeyman and Leonard C Harrison

Conclusions: Type 1 diabetes can be diagnosed in the preclinical stage. The recently described antibodies to glutamic acid decarboxylase and tyrosine phosphatase IA2 appear superior to ICA as screening tools for the preclinical diagnosis of type 1 diabetes.

MJA 1998; 169: 81-84
Progression to T1D with ICA > 20 JDFu
Risk increases with IAA in addition to ICA.
Risk of T1D increases with increase in number of antibodies
High risk for progression to T1D

- Multiple autoantibodies
- High titre antibodies to
  - IA2
  - Insulin
  - ZnT8
- Titre of GAD antibodies not predictive
Seroconversion to Multiple Islet Autoantibodies and Risk of Progression to Diabetes in Children

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Marian Rewers, MD, PhD
Olli Simell, MD, PhD
Tuula Simell, MPH, PhD
Johanna Lempainen, MD, PhD
Andrea Steck, MD
Christiane Winkler, PhD
Jorma Ilonen, MD, PhD
Riitta Veijola, MD, PhD
Mikael Knip, MD, PhD
Ezio Bonifacio, PhD
George S. Eisenbarth, MD, PhD†

![Graph showing the probability of progression to diabetes over follow-up time from seroconversion.](image)

<table>
<thead>
<tr>
<th>Probability of Progression to Diabetes, %</th>
<th>Follow-up From Seroconversion, y</th>
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<tr>
<td>0</td>
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<tr>
<td>20</td>
<td>5</td>
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<tr>
<td>60</td>
<td>15</td>
</tr>
<tr>
<td>80</td>
<td>20</td>
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</table>

<table>
<thead>
<tr>
<th>No. of events</th>
<th>No. at risk</th>
<th>Diabetes</th>
<th>Lost to follow-up</th>
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<tr>
<td></td>
<td>585</td>
<td>236</td>
<td>92</td>
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<td>95</td>
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<td>70</td>
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<tr>
<td></td>
<td>8</td>
<td></td>
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</tr>
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</table>
Using measures of beta cell function to define risk of progression to T1D
Standardize tests of residual beta cell function

Reproducibility of the First-Phase Insulin Response to Intravenous Glucose Is Not Improved by Retrograde Cannulation and Arterialization or the Use of a Lower Glucose Dose

CONCLUSIONS --- The intravenous glucose tolerance test is reproducible when performed by the same operator over a short time span. Reproducibility is not significantly improved by sampling from an arterialized, retrograde cannulated, contralateral hand vein. There is no case for changing the present ICARUS protocol to incorporate retrograde cannulation or low-dose (5 g/m²) glucose.
Low first phase insulin release in antibody positive first degree relatives is a strong predictor of progression.

Colman et al. MJA 1998; 169:81-84
Those with FPIR $\leq$ 50mU/L developed diabetes within 5 years

Colman et al. MJA 1998; 169:81-84
FPIR fell linearly over time in the antibody positive relatives who developed diabetes.

Colman et al. MJA 1998; 169:81-84
When does the autoimmune process begin?

What triggers the process?
Study of babies from birth

Australian BabyDiab Study

- over 500 at-risk babies followed at 6 monthly intervals from birth for development of islet immunity
Islet autoimmunity in infants with a Type I diabetic relative is common but is frequently restricted to one autoantibody

P. G. Colman, C. Steele, J. J. Couper, S. J. Beresford, T. Powell, K. Kewming, A. Pollard, S. Gellert, B. Tait, M. Honeyman, ...

- 14% positive for one antibody once
- 5% for a single antibody more than once
- 2.8% persistently positive
Antibodies generally detected after 12 months; IAA commonly first

<table>
<thead>
<tr>
<th>First antibody detected</th>
<th>Number of infants</th>
<th>Age at detection (months)</th>
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<tbody>
<tr>
<td>IAA</td>
<td>8</td>
<td>12 (× 3), 18, 24 (× 3), 30</td>
</tr>
<tr>
<td>GADA(\text{Ab})</td>
<td>5</td>
<td>6, 18, 36 (× 2), 54</td>
</tr>
<tr>
<td>IA2(\text{Ab})</td>
<td>2</td>
<td>18 (× 2)</td>
</tr>
<tr>
<td>IAA and GADA(\text{Ab})</td>
<td>5</td>
<td>6, 18 (× 2), 24, 30</td>
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<tr>
<td>IAA and IA2(\text{Ab})</td>
<td>2</td>
<td>6, 18</td>
</tr>
<tr>
<td>GADA(\text{Ab}) and IA2(\text{Ab})</td>
<td>2</td>
<td>12, 24</td>
</tr>
<tr>
<td>All three antibodies</td>
<td>1</td>
<td>18</td>
</tr>
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</table>
Infant 17 - developed T1D

- Male
- HLA DR 3,4
- FPIR
  - 36 months: 25mU/L
  - 42 months: 6mU/L
- Diabetes at 42 months

![Graph showing multiples of normal for IAA, GADAb, IA2Ab](chart.png)
Insulin resistance - important in pathogenesis of T1D

? A future target for altering the natural history
3773 1^{st} degree relatives of people with T1D screened for islet antibodies

Preclinical diabetes
104 relatives with $\geq 1$ islet antibody
followed with metabolic and antibody testing for median of 4.0 years

Matched for T1D risk factors
  Age
  Number of islet antibodies
  FPIR

Matched progressors = 21
Matched non-progressors = 21
Metabolic results:

- **Progressors**
- **Non-progressors**

**Fasting glucose (mmol/L)**
- Progressors: 5.3 ± 0.0
- Non-progressors: 4.7 ± 0.0

**Fasting insulin (mU/L)**
- Progressors: 12.6 ± 6.9
- Non-progressors: 6.9 ± 0.0

**HOMA-R**
- Progressors: 3.0 ± 0.0
- Non-progressors: 1.4 ± 0.0

**FPIR (mU/L)**
- Progressors: 115 ± 117
- Non-progressors: 115 ± 117

**p-values**: p = 0.007, p < 0.001, p < 0.001, p = NS
Islet-antibody positive relatives who progressed to T1D had
• higher fasting glucose,
• higher fasting insulin, and
• insulin resistance
in the pre-clinical phase

Fourlanos et al. Diabetologia 47: 1661-1667, 2004
Insulin resistance makes progression to diabetes more likely in antibody positive relatives ......

Does insulin resistance in early life have any association with development of islet autoimmunity?
Weight Gain in Early Life Predicts Risk of Islet Autoimmunity in Children With a First-Degree Relative With Type 1 Diabetes

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PETER A. BAGHURST, PHD²

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PETER G. COLMAN, PHD⁶

Diabetes Care 32: 94-99, 2009
Australian BabyDiab

At birth HLA typing on cord blood
6 monthly review from birth

• Length (if <2 years old) or height
• Weight
  - Measurements converted to Z score
• After 2 yrs of age BMI calculated and converted to Z score
• Dietary intake - home diary and face to face interview
• 46/548 (8.4%) developed islet autoimmunity during mean follow up of 5.7 years
• 12 progressed to diabetes at 4.2 ± 2.1 yrs
Weight z score

- A continuous predictor of islet autoimmunity
- Remained a continuous predictor after controlling for HLA type
  - HR 1.45 (CI 1.00-1.84) per unit increase in z score
- If weight z score dichotomized over time to $<0$ or $>0$ there was a significant difference in risk of islet autoimmunity
BMI z score

• Over time a continuous predictor of risk of islet autoimmunity
• Remained a continuous predictor after controlling for HLA type
Early weight gain in childhood predicts risk of early islet autoimmunity in children with a first degree relative with T1D

- Rapid weight gain may cause increased metabolic activity of β cells.
- Increased insulin production by cells upregulate GAD and Fas to Fas ligand.
- These cells more liable to destruction.
Changing genetic profile of T1D

Type 1 diabetes DNA Repository

• 100 multiplex families and ~350 simplex families
• DNA, family structure, demographics, antibody status
The Rising Incidence of Type 1 Diabetes Is Accounted for by Cases With Lower-Risk Human Leukocyte Antigen Genotypes

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Brian D. Tait, PhD³
Grant Morahan, PhD⁴

Margo C. Honeyman, PhD¹
Peter G. Colman, MD, FRACP²
Leonard C. Harrison, MD, FRACP, FRCPA, DSC¹

Diabetes Care 31: 1546-1549, 2008
Australian type 1 diabetes repository

- $n = 462$
- T1D onset $< \text{age } 18$ years
- Diagnosed between 1950 – 2005 (91% 1975 onwards)
- Median age of diagnosis 8.5 years
Increasing proportion of T1D cases with lower risk HLA genotypes over the decades.

Absolute increase in T1D cases is accounted for by cases with 'lower risk' HLA genes

<table>
<thead>
<tr>
<th>DRB1 Genotype</th>
<th>Proportion</th>
<th>Cases §</th>
<th>Proportion</th>
<th>Cases</th>
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<tbody>
<tr>
<td>DR3,4</td>
<td>44%</td>
<td>5.3</td>
<td>28%</td>
<td>6.5</td>
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<tr>
<td>DR3,3 and DR 4,4</td>
<td>12%</td>
<td>1.4</td>
<td>21%</td>
<td>4.9</td>
</tr>
<tr>
<td>DR3,X and DR 4,X</td>
<td>39%</td>
<td>4.4</td>
<td>48%</td>
<td>11.1</td>
</tr>
<tr>
<td>DRX,X</td>
<td>1%</td>
<td>0.1</td>
<td>3%</td>
<td>0.7</td>
</tr>
</tbody>
</table>

Incidence 11.3/100,000* Incidence 23.2/100,000
Changing T1D risk and genetics

The rising incidence and decreasing age at diagnosis of T1D is accounted for by the impact of environment on children with lower risk HLA class II genes, who previously would not have developed diabetes in childhood.

The contribution of HLA genes to T1D has changed but not lessened over time. Indeed, genetic susceptibility to T1D is no less relevant as more individuals fall under the shadow of a ‘diabetogenic’ environment.
Expanding the autoimmune diabetes pathogenesis jigsaw

- Lower risk HLA genes increasing in T1D
- Higher BMI associated with development of islet autoimmunity
- Insulin resistance is a risk factor for progression to T1D
- LADA characterised by Adiposity in association with lower risk HLA genes
So, we can identify people in the preclinical phase - can we prevent them developing T1D?
When can we intervene?

- Prior to development of autoimmunity
  - Genetically at risk

- After development of autoimmunity with preserved glucose tolerance or abnormal glucose tolerance (so called ‘silent’ diabetes)

- At diagnosis - to preserve function
Natural History of T1D

- Genetic at-risk
- Environmental trigger(s)
- Islet antibody positive
- First phase insulin response impaired

- Genetic predisposition
- Insulitis beta-cell damage
- Pre-diabetes
- Diabetes

0% - 100% BETA CELLS

TIME
Prior to development of autoimmunity

TRIGR
NIP
PRE POINT
Trial to Reduce Insulin-Dependent Diabetes in the Genetically at Risk

Nutritional Primary Prevention of Type 1 Diabetes in Children
'Dietary intervention during infancy appears to have a long-lasting effect on markers of beta-cell autoimmunity - markers that may reflect an autoimmune process leading to type 1 diabetes'
THE APPEARANCE OF AT LEAST ONE AUTOANTIBODY

A

Cumulative Survival without ≥1 Autoantibody (%)

Age (yr)

P = 0.02

No. at Risk
Casein hydrolysate 90 85 81 78 72 66 62
Control 107 98 95 88 75 76 69

APPEARANCE OF TWO OR MORE AUTOANTIBODIES

B

Cumulative Survival without ≥2 Autoantibodies (%)

Casein hydrolysate
Control

P = 0.07

Age (yr)

0 1 2 3 4 5 6 7 8 9 10

No. at Risk
Casein hydrolysate 90 85 81 78 72 66 62
Control 107 98 95 88 75 76 69

Pilot

Nutritional Intervention to Prevent Type 1 Diabetes (NIP Diabetes)

**Plan:** Use of an omega 3 fatty acid (Docosahexanoic acid or DHA) to prevent the initial autoimmune process.

DHA supplementation in:
- the last trimester of pregnancy
- the first 6 months after birth
II) Background: DHA

Docosahexanoic acid (DHA)

- Omega-3 fatty acid
- Important component of cell membranes
- Found in all tissues; most abundant in neural, retinal and heart tissue
- Important in infant development and cardiovascular health
Infant RBC DHA Levels

Infant RBC DHA Levels (mg/dL)

<table>
<thead>
<tr>
<th>Months</th>
<th>Control (mg/dL)</th>
<th>Treatment (mg/dL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>6</td>
<td>42.8 (29)</td>
<td></td>
</tr>
<tr>
<td>12</td>
<td>42.3 (14)</td>
<td></td>
</tr>
<tr>
<td>18</td>
<td>29.2 (26)</td>
<td>46.9 (22)</td>
</tr>
</tbody>
</table>

* = p<0.001

Type 1 Diabetes TrialNet
Nutritional Intervention to Prevent (NIP) Type 1 Diabetes
A Pilot Trial

H. Peter Chase, MD, Ellen Lescheck, MD, Lisa Rafkin-Mervis, MS, CDE, Heidi Krause-Steinrauf, MS, Sonia Chritton, MS, Smita M. Asare, Sara Adams, Jay S. Skyler, MD, Michael Clare-Salzler, MD, and the Type 1 Diabetes TrialNet NIP Study Group


Interventions in this group are feasible
Screening to determine diabetes risk genes

We do a screening test to find children who have a high risk of developing diabetes. All children from Germany, Austria, the UK, the USA and Canada can participate if they

- are between 18 months and 7 years of age and
- have at least one brother or sister or both parents with type 1 diabetes.

The Pre-POINT study is the first study that offers an immunization-like treatment to delay or even prevent autoimmunity and type 1 diabetes. The preventative treatment with insulin is intended to stop the development of diabetes autoantibodies in children with high genetic risk. The aim of the study is to find the most appropriate dose of the insulin to do this.

The child will take the insulin by mouth as a powder on a daily basis. Insulin given in these ways does NOT lower blood glucose, but it is supposed to influence the immune system, similar to an immunization.
Modulating the Natural History of Type 1 Diabetes in Children at High Genetic Risk by Mucosal Insulin Immunization

Peter Achenbach, MD, Jennifer Barker, MD, and Ezio Bonifacio, PhD

Current Diabetes Reports 8:87-93, 2008

'Prepoint' Trial

Royal Melbourne Hospital
Prevention trials

Those who have already developed autoimmunity
Natural History of T1D

- **GENETICALLY AT-RISK**
- **ENVIRONMENTAL TRIGGER/S**
- **ISLET ANTIBODY POSITIVE**
- **FIRST PHASE INSULIN RESPONSE IMPAIRED**

**Timeline**
- **TIME**
- **BETA CELLS**
  - **GENETIC PREDISPOSITION**
  - **INSULITIS BETA-CELL DAMAGE**
  - **PRE-DIABETES**
  - **DIABETES**

0% to 100% along the vertical axis.
Effects of Oral Insulin in Relatives of Patients With Type 1 Diabetes

The Diabetes Prevention Trial–Type 1

THE DIABETES PREVENTION TRIAL–TYPE 1
STUDY GROUP

Diabetes Care 28:1068–1076, 2005
DPT-1 Oral Study - Time to Diabetes Subset: IAA > 80 nU/ml

Survival Distribution Function

P-Value = 0.015 (Log Rank Test)
Number at Risk

<table>
<thead>
<tr>
<th>Years Followed</th>
<th>Oral Insulin</th>
<th>Oral Placebo</th>
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<tr>
<td>0</td>
<td>133</td>
<td>121</td>
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<tr>
<td>1</td>
<td>104</td>
<td>96</td>
</tr>
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<td>2</td>
<td>86</td>
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<tr>
<td>5</td>
<td>23</td>
<td>12</td>
</tr>
</tbody>
</table>

Diabetes Care 2005; 28:1068-76
Insulin Effect Most Evident in Subjects with Baseline IAA ≥ 300

Projected 10 year delay

Oral Insulin
Placebo
Treated
Control

Proportion Free of Diabetes

Log-rank P=0.01
Pet>Pr. P=0.01
Hazard Ratio: 0.41 (0.21, 0.80)

N=63 (Ins.) and 69 (Plac.)

Years Followed
Long term Protection Afforded in Subjects with Baseline IAA > 80 nU/ml (1994-2009)

Survival Distribution Function

P-Value = 0.052 (Log Rank Test)

Number at Risk:
130 127 117 107 89 73 60 47 43 37 28 20 16 7
133 127 112 88 73 66 55 43 34 25 16 12 7

Years Followed

Strata:
- Oral Insulin
- Oral Placebo

Diabetes Care (in press, 2011)
A randomized double-blind, placebo-controlled trial of intranasal insulin (440 units) in children and young adults at risk of T1D
INIT II Study Design

Screening

Staging
(2 visits)

Baseline Visit
(Randomisation)

Placebo

440IU Insulin

Trial Treatment Visits
(3-monthly for 1 year)

Follow up Visits
(6-monthly for 4 years, then yearly)
Sample size

- 5-year risk for relatives with $\geq$ two islet autoantibodies, above threshold FPIR and normal OGTT, for progression to diabetes is 40%.

- Expectation of reducing diabetes development by 50%, i.e. a 5-year risk for progression to diabetes of 20%
Percent positive (n=8731 tested)
INIT II - staging

- Oral glucose tolerance - must be normal (WHO criteria)

- Intravenous glucose tolerance test for measurement of first phase insulin release (must be above 1st percentile for normals)
INIT II staging - OGTT (n=95)
INIT II staging - OGTT

21% diabetic or impaired glucose tolerance
A new concept - ‘silent’ type 1 diabetes

Type 1 diabetes prior to the onset of symptoms

??how should it be managed
Preserving β cell function at diagnosis
Natural History of T1D

100% Genetically At-Risk

0% Environmentally Triggered

First Phase Insulin Response Impaired

Genetic Predisposition

Insulitis Beta-Cell Damage

Pre-Diabetes

Diabetes

Beta Cells

Time
TrialNet Interventions in New Onset T1D

- Mycophenolate Mofetil +/- Anti-CD25
- Anti-CD20 (Rituximab)
- CTLA4-Ig (Abatacept)
- Anti-CD3
- GAD-Alum
- Meticulous Metabolic Control
- Canakinumab
Study Design

• Randomized multicentre controlled clinical trials

• Eligibility
  - Within 3 months of diagnosis
  - Aged 6-45 yr
  - Stimulated C-peptide >0.2nmol/L
  - Detectable antibodies (mIAA, GAD, IA2 or ICA

• Double blinded

• Stratification by centre

• Randomization (usually 2:1)

• Carefully calculated sample size
Primary outcome measure - adjusted geometric mean C-peptide AUC

- 1 year difference between placebo and investigative agent from the first 2hr of the 4hr MMTT
- Adjusted for age, baseline C-peptide, gender, treatment assignment
Secondary outcome measures

- Geometric mean C-peptide AUC
  - 4-hr MMTT at baseline & month 12
  - 2-hr MMTT at months 3, 6
- Rate of change of C-peptide (decay slope)
- Time to first stimulated C-peptide <0.2nmol/L
- HbA1c at months 3, 6, 9, 12
- Insulin units/kg at months 3, 6, 9, 12
- Subgroup analyses
- Safety and mechanistic studies
Canakinumab

- Binds IL-1β to hinder receptor binding
- Long half life (~4 weeks)
- Subcutaneous

Canakinumab - no effect on C-peptide

CTLA4 Ig (Abatacept)

Without Abatacept

With Abatacept

CD80/86
CD28
Activated T cell

Abatacept

Abatacept - Study groups

• Two Groups
  – Abatacept (CTLA4-Ig, Orencia) 10 mg/kg; maximum 1000 mg/dose
  – Placebo

• 27 intravenous infusions over 2 years
  – No pre-medication
  – Infused as outpatient over 30 minutes
Abatacept - c-peptide from 2-hr AUC mean over time

Abatacept in newly diagnosed
Abatacept – HbA1c (%) over time

24 months: 47.2% abatacept, 25.8% placebo A1c < 7%

Aggregate p=0.002; adjusted for baseline A1c p=0.0071

Time on Study (months)
Abatacept – insulin dose over time
Abatacept

• Initially slowed decline in beta cell function in recent-onset T1D; difference from placebo was maintained through 36 months

• Might be useful in
  - Prevention studies in high risk people
  - As one component in studies using a combination of different treatment strategies
CTLA-4 Ig (Abatacept) FOR PREVENTION OF ABNORMAL GLUCOSE TOLERANCE AND DIABETES IN RELATIVES AT-RISK FOR TYPE 1 DIABETES MELLITUS
Prediction

• Antibody testing identifies risk of T1D in first degree relatives with high sensitivity and specificity
• Assays are well standardized
• Multiple antibodies and high antibody titres denote higher risk
• Improvement of antibody tests is required
• ?when to test
Prevention and preservation of beta cells

- Early evidence suggests efficacy of some agents, but still not for routine use
- Continuing strong trial activity prior to and at diagnosis