TYPE 1 DIABETES: NEW AND EMERGING THERAPEUTIC STRATEGIES TO ADDRESS UNMET NEEDS

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DISCLOSURES

STEVEN V. EDELMAN, MD
• Board Member: Senseonics, TeamType1
• Medical Advisory Board: AstraZeneca, Companion Medical, Lexicon, Lilly USA, LLC, Mannkind Corporation, Merck, Sanofi-aventis U.S. Inc.
• Speaker’s Bureau: AstraZeneca, Lilly USA, LLC, MannKind Corporation, Merck, Sanofi-aventis U.S. Inc.

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• Research Funding: Novo Nordisk
TOPICS TO BE DISCUSSED

Unmet needs in type 1 diabetes

Historical perspective of type 1 diabetes

State of type 1 diabetes care in 2019

Continuous glucose monitoring (CGM)

UNMET NEEDS IN TYPE 1 DIABETES

• Unpredictable glycemia variability (GV), decreased time in range (TIR)
• Reaching A1c goal without hypoglycemia
• Controlling blood pressure
• Preventing and controlling weight gain
• Emotional burden of living with type 1 diabetes for the individual and his/her family
Ted Ryder
5 months after starting insulin

FAST FORWARD TO T1D CARE IN 1970

- NPH and regular insulins used only once or twice a day.
- Urine testing only
- No A1c test
- No pumps or pens
- No insulin analogs
- No CGM
- No Apps
PREVALENCE OF T1D INCREASING IN US

- 1.3 million people in U.S. currently have T1D\(^1\)
  - 1 million adults ≥ 20 years
- 21% increase in prevalence of T1D in people < 20 years between 2001-2009\(^2\)
- 40,000 people diagnosed each year in U.S.\(^2\)
- 5 million people in U.S. expected to have T1D by 2050\(^2\)
Type 1 is an autoimmune disease: the immune system attacks healthy beta cells.

Natural Progression is months to a few years.

Natural History and Cause of Type 1 Diabetes:
- Putative Trigger
- Immune System Dysfunction
- Circulating Auto Antibodies (ICA, GAD)
- Genetic predisposition
- Damage to the cells of the pancreas
- Pre-diabetes
- Diabetes

Symptoms: LADA

Time = months to a few years.
LATENT AUTOIMMUNE DIABETES IN ADULTS (LADA)

- The most missed diagnosis in diabetes
- Type 1 diabetes can occur at any age
- Slower beta-cell destruction (may respond briefly to oral agents)
- Typically does not have features of the Metabolic Syndrome
- Blood test positive for type 1 diabetes (GAD auto antibodies)

Gary Hall Jr.
Olympic Gold Medalist
World Record Holder

AGE AT DIAGNOSIS OF T1D

You can get type 1 diabetes at any age!

Beck RW, Tamborlane WV, Bergenstal RM, Miller KM, Dubose SN, Hall CA.
First-degree family member with T1D

- Yes: 16%
- No: 84%

FAMILY HISTORY OF T1D


RACE/ETHNICITY

- CAUCASIAN: 81%
- White Non-Hispanic: 5%
- Black Non-Hispanic: 8%
- Hispanic or Latino: 3%
- Native Hawaiian/Other Pacific Islander: 1%
- Asian: 1%
- American Indian/Alaskan Native: 1%
- More than One Race: 1%
CONSEQUENCES OF WEIGHT GAIN

- Excess weight gain associated with risk factors for cardiovascular disease, including increased
  - Lipid levels
  - Blood pressure levels
  - Waist circumference
  - Metabolic syndrome
VARIABLES THAT AFFECT GLUCOSE LEVELS

- Simple Carbs
  - Fast
- Complex Carbs
  - Slow
- Fatty Meal
  - Very Slow
  - Still there the next day
- French Meal
  - See French Meal
- Gastroparesis
- Constipation
- Exercise
  - Rapid
- Blood Glucose Levels

- Brain function
- Digestion
- Sustained

- Insomnia
- Exposure to cold
- Menstruation
- Illness
- Medication
- Emotion
- Stress
- Sex
- Time change
- Caffeine
- Smoking


ONLY ~30% OF TYPE 1S REACH ADA GOAL OF AN A1C LESS THAN 7%

- A1c Goal = <8.5%
  - 65%
- A1c Goal = <8.0%
  - 46%
- A1c Goal = <7.5%
  - 23%
- A1c Goal = <7.0%
  - 20%
- 30%
- 27%
- 34%

THE A1C REPRESENTS ONLY THE AVERAGE BLOOD GLUCOSE OVER TIME (ALL TREATED WITH FAST-ACTING ANALOGUES)

Mean A1C=6.7%

24-hour CGMS glucose sensor data
Type 1 diabetes (N=9)

Glucose Concentration (mg/dL)

DESPITE FOLLOWING ALL OF THE RULES

1. Unexpected highs
2. Unexpected lows
3. Carb:Insulin ratio not working consistently
4. Correction Factor not working consistently
5. Not responding to insulin and exercise consistently

IT IS ALL ABOUT “TIME IN RANGE”
KEEPING THE GLUCOSE LEVELS BETWEEN 70 AND 180 MG/DL

1. 1st priority is getting a CGM and educate your patients to respond to the trend arrows.
2. Bolus calculations are more than just the carbohydrates and static glucose readings
3. In addition to getting the A1c below 7%, try to reduce the daily glucose fluctuations in your patients (hyper- and hypoglycemia)
4. The insulin regimen should mimic what happens in a non-diabetic state


SMART PHONE CLARITY APP

Mean glucose value
Standard Deviation
Time in Range
24 hour multiday profile
G6

- No calibration required
- 10 day sensor life
- Predictive low alerts
- No interference with acetaminophen
- Auto inserter
- Medicare Approved
EVERSENSE

**Implantable Continuous Glucose Monitor**

- **Sensor**
  - Sensor lasts up to 90 days
  - No weekly sensor insertion
  - No open wound

- **Smart Transmitter**
  - Removable and rechargeable
  - On-body vibe alerts
  - Gentle, daily adhesive patch

- **Mobile App**
  - No extra device to carry
  - iOS and Android platform
  - Alarm settings & reports

**EVERSENSE IMPLANTABLE CGM**

[Image of a man with the CGM implant and data on his mobile app]
GUARDIAN CONNECT

- Predictive high alerts
- Predictive low alerts
- Requires calibration
- 6-day wear
- Need to confirm with fingerstick when dosing

https://www.medtronic-diabetes.co.uk/minimed-system/minimed-640g-system; accessed April 2017

FREESTYLE LIBRE FLASH
IS OR INTERMITTENT SENSING

- 2 hour warm-up time
- Lasts 2 weeks
- Swipe to get a number
- Trend arrows
- No calibration
- No alerts or alarms
- No sharing features
Hypoglycemia

Using CGM trend arrows to make insulin adjustments

Fast, ultra fast and new long-acting basal insulins

Evaluating basal doses and time of injections

SEVERE HYPOGLYCEMIA – SERIOUS AE IN T1D DUE TO TOO MUCH INSULIN


<table>
<thead>
<tr>
<th>Age (years)</th>
<th>Pump</th>
<th>MDI</th>
<th>Overall</th>
</tr>
</thead>
<tbody>
<tr>
<td>18-25</td>
<td>5</td>
<td>6</td>
<td>6</td>
</tr>
<tr>
<td>26-49</td>
<td>6</td>
<td>9</td>
<td>8</td>
</tr>
<tr>
<td>&gt; 50</td>
<td>7</td>
<td>8</td>
<td>8</td>
</tr>
</tbody>
</table>
A SINGLE BG AT ONE POINT IN TIME LACKS IMPORTANT INFORMATION

- No insulin
- Watch and maybe get some carbs
- Take a larger than usual dose

Pump and meter software suggests the same either way

Severe Hypoglycemia and A1C: DCCT\textsuperscript{15} (1993), JDRF\textsuperscript{2} (2008), and STAR 3\textsuperscript{16} (2010) Studies

- DCCT (intensive therapy): 62 per 100 pt-yrs, A1C (6.5 yr): 9.0% $\rightarrow$ 7.2%
- JDRF CGM: 20.0 per 100 pt-yrs; A1C (6 mo): 7.5% $\rightarrow$ 7.1%
- STAR 3 MDI (all ages): 13.5 per 100 pt-yrs; A1C (1 yr): 8.3% $\rightarrow$ 8.1%
- STAR 3 SAP (all ages): 13.3 per 100 pt-yrs; A1C (1 yr): 8.3% $\rightarrow$ 7.5%
### HOW CGM AND TRENDING INFORMATION CAN AFFECT OUR DECISIONS (CF/I:CHO)

<table>
<thead>
<tr>
<th>Indicator</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Constant</td>
<td>Your glucose is steady (not increasing/decreasing more than 1 mg/dL each minute)</td>
</tr>
<tr>
<td>Slowly rising</td>
<td>Your glucose is rising 1-2 mg/dL each minute</td>
</tr>
<tr>
<td>Rising</td>
<td>Your glucose is rising 2-3 mg/dL each minute</td>
</tr>
<tr>
<td>Rapidly rising</td>
<td>Your glucose is rising more than 3 mg/dL each minute</td>
</tr>
<tr>
<td>Slowly falling</td>
<td>Your glucose is falling 1-2 mg/dL each minute</td>
</tr>
<tr>
<td>Falling</td>
<td>Your glucose is falling 2-3 mg/dL each minute</td>
</tr>
<tr>
<td>Rapidly falling</td>
<td>Your glucose is falling more than 3 mg/dL each minute</td>
</tr>
<tr>
<td>No arrow</td>
<td>No Rate of Change Information: The Receiver cannot always calculate how fast your glucose is rising or falling</td>
</tr>
</tbody>
</table>


### MEAN CHANGE IN INSULIN DOSE BASEDON 2 ARROWS UP: SURVEY OF 300 CGM USERS

<table>
<thead>
<tr>
<th>Increase (mg/dL)</th>
<th>Insulin Dose (units)</th>
</tr>
</thead>
<tbody>
<tr>
<td>3.0</td>
<td>220</td>
</tr>
<tr>
<td>6.8</td>
<td>220</td>
</tr>
</tbody>
</table>

HOW CGM AND TRENDING INFORMATION CAN AFFECT DOSING DECISIONS

<table>
<thead>
<tr>
<th>Rate of Change</th>
<th>Description</th>
<th>Dose Change</th>
</tr>
</thead>
<tbody>
<tr>
<td>▲▲▲▲</td>
<td>Rapidly rising: Your glucose is rising more than 3 mg/dL each minute</td>
<td>6.8 units</td>
</tr>
<tr>
<td>▲▲▲</td>
<td>Slowly rising: Your glucose is rising 1-2 mg/dL each minute</td>
<td>3.0 units</td>
</tr>
<tr>
<td>▲▲</td>
<td>Rising: Your glucose is rising 2-3 mg/dL each minute</td>
<td>1.5 units</td>
</tr>
<tr>
<td>▲</td>
<td>Constant: Your glucose is steady (not increasing/decreasing more than 1 mg/dL each minute)</td>
<td>No change in calculation</td>
</tr>
<tr>
<td>▼</td>
<td>Falling: Your glucose is falling 2-3 mg/dL each minute</td>
<td>1.5 units</td>
</tr>
<tr>
<td>▼▼▼</td>
<td>Slowly falling: Your glucose is falling 1-2 mg/dL each minute</td>
<td>3.0 units</td>
</tr>
<tr>
<td>▼▼▼▼</td>
<td>Rapidly falling: Your glucose is falling more than 3 mg/dL each minute</td>
<td>6.8 units</td>
</tr>
<tr>
<td>▼▼▼▼▼</td>
<td>No Rate of Change Information: The Receiver is not in a state of steady, rising, or falling.</td>
<td>140% Mean Increase</td>
</tr>
</tbody>
</table>

CASE: JEREMY

- 35 year old male with type 1 diabetes for 20 years
- CHO to insulin ratio 10:1
- CF 1:30 goal 120 mg/dl

Post “Snack” BS of 220 mg/dL at 4:00 p.m.
(snack at 3:30 p.m., no insulin given with snack)
CASE: JEREMY (CONTINUED)

• Jeremy’s CGM Guidelines
  – Correction factor 1:30
  – Target glucose 120 mg/dL
  – 220-120/30 = 3.3 units

Note: A blood sugar of 220 does not lead to any symptoms

WHICH OPTION BELOW IS THE BEST SUGGESTION FOR JEREMY TO FOLLOW AT 4:00 PM?

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Watch and wait (give no additional insulin)</td>
</tr>
<tr>
<td>B</td>
<td>Walk for an hour at a brisk pace</td>
</tr>
<tr>
<td>C</td>
<td>Give a correction dose of 3.3 units</td>
</tr>
<tr>
<td>D</td>
<td>Give a correction dose greater than 3.3 units</td>
</tr>
</tbody>
</table>
ADJUST INSULIN DOSE BASED ON ANTICIPATED GLUCOSE IN 30 MINUTES

<table>
<thead>
<tr>
<th>Adjusted Glucose Value for Dosing</th>
<th>Add 50 mg/dl</th>
<th>Add 75 mg/dl</th>
<th>Add 100 mg/dl</th>
</tr>
</thead>
<tbody>
<tr>
<td>No Adjustment. Dose for current glucose value.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adjust UP — current value plus 25-50 mg/dl. Dose for adjusted value.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adjust UP — current value plus 50-75 mg/dl. Dose for adjusted value.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adjust UP — current value plus 75-100 mg/dl. Dose for adjusted value.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adjust DOWN — current value minus 25-50 mg/dl. Dose for adjusted value.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adjust DOWN — current value minus 50-75 mg/dl. Dose for adjusted value.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adjust DOWN — current value minus 75-100 mg/dl. Dose for adjusted value.</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Wait until trend arrow becomes horizontal

BLOOD GLUCOSE AFTER A MEAL WHEN BOLUS GIVEN 20 MINUTES BEFORE, AT START, OR 20 MIN AFTER THE MEAL
Both dietary fat and protein increase post meal glucose concentrations

Four test breakfasts with identical carbohydrate content, but varying protein and fat quantities: same insulin dose

- High fat/high protein
- High fat/low protein
- Low fat/high protein
- Low fat/low protein

Smart, Evans, O’Connell, Mckillop, Lopez, Davis, King. Both Dietary Protein and Fat Increase Postprandial Glucose Excursions in Children with Type 1 Diabetes, and the Effect is Additive. Diabetes Care 2013;36:3897

64 year old male with T1D for 30 years on a T1D regimen

What is/are the possible causes of this patient's glucose profiles overnight?

A. Needs more basal insulin
B. Needs to be more consistent in his dinner meals/times
C. He has gastroparesis
D. All of the above
PHYSIOLOGIC INSULIN, GLUCAGON AND AMYLIN SECRETION

Liver
Portal Vein
Systemic Circulation
Pancreas
Insulin
Amylin
Glucagon
Beta Cell
Alpha Cell

PHYSIOLOGIC INSULIN SECRETION AND GLUCOSE LEVELS IN HEALTHY SUBJECTS

Insulin (µU/mL)

Glucose (mg/dL)

Basal Insulin: HGO (40 to 60% of TTD)
Bolus Insulin (40 to 60% of TTD)
Basal Glucose

GENERIC AND TRADE NAMES: INSULIN

<table>
<thead>
<tr>
<th>Generic Name</th>
<th>Trade Name</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fast-Acting Insulin</td>
<td>Regular</td>
</tr>
<tr>
<td></td>
<td>U-500 Regular</td>
</tr>
<tr>
<td></td>
<td>Aspart</td>
</tr>
<tr>
<td></td>
<td>Faster Acting Aspart</td>
</tr>
<tr>
<td></td>
<td>Glulisine</td>
</tr>
<tr>
<td></td>
<td>Lispro (U-100 and U-200)</td>
</tr>
<tr>
<td></td>
<td>Follow on biologic lispro</td>
</tr>
<tr>
<td></td>
<td>Inhaled Insulin</td>
</tr>
<tr>
<td></td>
<td>Humulin R, Novolin R</td>
</tr>
<tr>
<td></td>
<td>Humulin R U-500</td>
</tr>
<tr>
<td></td>
<td>NovoLog</td>
</tr>
<tr>
<td></td>
<td>Fiasp</td>
</tr>
<tr>
<td></td>
<td>Apidra</td>
</tr>
<tr>
<td></td>
<td>Humalog</td>
</tr>
<tr>
<td></td>
<td>Admelog</td>
</tr>
<tr>
<td></td>
<td>Afrezza</td>
</tr>
<tr>
<td>Basal Insulin</td>
<td>Intermediate-Acting: NPH</td>
</tr>
<tr>
<td></td>
<td>Long-Acting: Detemir</td>
</tr>
<tr>
<td></td>
<td>Glargine (U-100)</td>
</tr>
<tr>
<td></td>
<td>Glargine (U-300)*</td>
</tr>
<tr>
<td></td>
<td>Degludec (U-100/200)*</td>
</tr>
<tr>
<td></td>
<td>Follow on biologic glargine (U-100)</td>
</tr>
<tr>
<td></td>
<td>Humulin N</td>
</tr>
<tr>
<td></td>
<td>Novolin NPH</td>
</tr>
<tr>
<td></td>
<td>Levemir</td>
</tr>
<tr>
<td></td>
<td>Lantus</td>
</tr>
<tr>
<td></td>
<td>Toujeo*</td>
</tr>
<tr>
<td></td>
<td>Tresiba*</td>
</tr>
<tr>
<td></td>
<td>Basaglar</td>
</tr>
</tbody>
</table>

INHALED INSULIN

- Better post meal glucose values
- Less delayed hypoglycemia

FASTER-ACTING ASPART (ADDITION OF L-ARGININE AND NIACINAMIDE FOR FASTER ABSORPTION)

2 hour PG levels in T1D on pump therapy after a standardized meal comparing Aspart with Faster Aspart

![Graph](source)

Bode et al DTT Vol 19 2017

TWO NEW BASAL INSULINS RECENTLY ADDED TO LIST OF OPTIONS

BOTH APPROVED BY THE FDA AND NOW AVAILABLE FOR PATIENTS

1. U-300 glargine a long-acting basal insulin

2. U-100 and U-200 degludec a long-acting basal insulin

BENEFITS OF U-300 GLARGINE AND DEGLUDEC IN TYPE 1 DIABETES

- Less intra-subject variability
- Less hypoglycemia
- Less weight gain
- Flat, stable and prolonged action greater than 24 hours
- Tell patients it takes 4 to 5 days to reach equilibration and they may need correction doses
- 1 to 1 conversion from prior basal dose (patients switching from U-100 to U-300 glargine may need ~15% more)
- Both insulins come in easy to use pens


GLUCOSE INFUSION RATE IN SUBJECTS WITH TYPE 1 DIABETES INSULIN GLARGINE U-300

50 T1D subjects underwent two euglycemic clamp studies after six days of receiving insulin glargine U-300

PHARMACODYNAMICS OF INSULIN DEGLUDEC
U-100 AND U-200
IN PATIENTS WITH T2DM: SAME TIME COURSE OF ACTION

U-100 Formulation\(^1,b\)

- 0.8 U/kg
- 0.6 U/kg
- 0.4 U/kg

U-200 Formulation\(^2,c\)

- 0.6 U/kg

GIR, mg/kg/min

Time, hours

0 4 8 12 16 20 24

0 1 2 3 4 5

3. Glucose clamp study in patients with T2DM (n = 49).

TOPICS TO BE DISCUSSED

- Pumps verses multiple daily injections
- Other adjunctive therapies for type 1 diabetes
- What does the future hold?
BASAL/BOLUS OR MDI INSULIN REGIMEN WITH RAPID AND LONG-ACTING ANALOGS/INHALED INSULIN

**Breakfast**

- **Insulin Action**
  - Glulisine
  - Aspart or Faster Acting Aspart or Lispro or Inhaled Insulin

**Lunch**

- **Insulin Action**
  - glargine and degludec

**Dinner**

- **Insulin Action**
  - Basal

**Time**

- 4:00
- 8:00
- 12:00
- 16:00
- 20:00
- 24:00
- 4:00
- 8:00

75% of Type 1S

SOFTWARE PROGRAMS AS PUMPS

- I: Carb ratio
- Correction factor
- Insulin log
- Cloud based
LET YOUR PATIENTS PICK THE PUMP

- Animas Vibe G4 (Discontinued)
- t:slim G6/X2
- 630/670G/530G
- OmniPod

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INSULIN PUMPS: ADVANTAGES

- **Improved glycemic control**
  - More precise, physiologic insulin delivery
  - Greater ability to handle dawn phenomenon, stress and other conditions that alter insulin requirements
  - “Smart features” help to estimate insulin doses and reduce errors, i.e. stacking insulin

- **In some situations (but not all) freedom and flexibility in lifestyle**
  - Eliminate multiple daily injections (1 stick every 3 days)
  - Very easy to respond to CGM results
  - Reduce restrictions on eating, exercise and sleeping patterns; could have the same benefits with MDI
  - Greater flexibility with sports, travel, work schedule and other activities (not with water sports)

---


PUMP VS. MULTIPLE DAILY INJECTIONS?

It comes down to personal choice!

TESTING THE BASAL RATE IN TYPE 1

Testing Overnight
1. Ask the patient have an early dinner, make sure the post prandial BS is between 140 and 180mg/dl (may need a correction dose) with a horizontal trend arrow
2. Fast until the next morning
3. If not on a CGM then he/she needs to test the BS every few hours

Testing During The Day (different day than testing pm)
1. Ask the patient if he/she can skip breakfast and fast as long as possible.
2. If patient wants to eat a small breakfast then make sure the post breakfast BS is between 140-180mg/dl with a horizontal trend arrow
TESTING A BASAL SEGMENT IN T1D:
FOUNDATION OF ANY INSULIN REGIMEN

0.75 U/hr

https://mysugr.com/basal-rate-testing/

194
mg/dL
Average glucose (CGM)

84
mg/dL
Standard deviation (CGM)

Is this basal dose right?

Test Results:
- Average glucose: 194 mg/dL
- Standard deviation: 84 mg/dL
- Hypoglycemia risk: 55%
- Time in range: 40%
- Days with CGM data: 93%
- Avg. calibrations per day: 1.4

Graph showing glucose levels over a 24-hour period.
What is the best treatment option to help this patient with his overnight values?

A. Decrease the basal insulin
B. Switch the U-100 glargine for U-300 glargine or degludec
C. Have a larger bedtime snack
D. Do not exercise after 7pm
ADJUNCTIVE THERAPIES FOR PEOPLE WITH TYPE 1 DIABETES

- Amylin Analog (Pramlintide)
- Incretins (GLP-1 RA) *
- SGLT-2 Inhibitors*
- DPP4 Inhibitors*
- Metformin*  
*Medications FDA approved only in type 2 diabetes at the current time

DPP-4 INHIBITORS IN T1D

- No statistically significant differences compared to placebo

METFORMIN IN T1D

- No statistically significant differences compared to placebo in A1c, hypoglycemia and DKA
- Slight reduction in weight and insulin dose

Garg et al. Endocrine Practice, 2013
REGULATION OF BLOOD GLUCOSE LEVELS AFTER MEALS BY AMYLIN

- Amylin is co-released with insulin after ingestion of food
- Stomach motility is normalized
- Reduces the appetite and leads to weight loss
- Suppression of glucagon levels from the alpha cells of the pancreas
- The reduced glucagon levels help to control excessive glucose production by the liver

PRAMLIINTIDE REDUCES FBG, PPG AND GLUCOSE FLUCTUATIONS

Clinical Practice Study, 120 µg SYMLIN
bf, breakfast; lu, lunch; di, dinner
N=166; *p-values for all data points <0.05
Data on file, Amylin Pharmaceuticals, Inc.
PRAMLIINTIDE + INSULIN: EFFECT ON SUSTAINED WEIGHT LOSS

Insulin alone: weight gain

insulin plus pramlintide: weight loss

49YO WOMAN WITH T1D X 33 YEARS, A1C 9%
AVG GLUCOSE 176.9 / S.D. 66.3
AFTER 3 MONTHS ON PRAMlintide, A1C 7.4%, LOST 12 LBS. AVG GLUCOSE 122.4 / S.D. 30.4

GLP-1 RECEPTOR AGONIST IN T1D

- There were small very early studies with exenatide
- One large well controlled study looking at liraglutide
- Many of the clinical effects in type 1 are similar to what is seen with SGLT ½ inhibitors
- No agent is actively being studied for FDA approval in type 1 diabetes
### Recap of Key Results of Liraglutide in T1DM

<table>
<thead>
<tr>
<th></th>
<th>Adjunct One&lt;sup&gt;1&lt;/sup&gt;</th>
<th>Adjunct Two&lt;sup&gt;2&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>HbA1c change</strong> (placebo-adjusted)</td>
<td>Mean decrease up to 0.2%</td>
<td>Mean decrease up to 0.35%</td>
</tr>
<tr>
<td><strong>Insulin dose change</strong> (placebo-adjusted)</td>
<td>Mean decrease up to 9%</td>
<td>Mean decrease up to 10%</td>
</tr>
<tr>
<td><strong>Body weight loss</strong> (placebo-adjusted)</td>
<td>Mean decrease up to 5 kg</td>
<td>Mean decrease up to 5 kg</td>
</tr>
<tr>
<td><strong>Severe hypoglycaemia</strong></td>
<td>Numerically lower in Lira vs placebo</td>
<td>No apparent difference</td>
</tr>
<tr>
<td><strong>Symptomatic hypoglycaemia</strong></td>
<td>Lira 1.8 mg and Lira 1.2 mg higher vs placebo</td>
<td>Lira 1.2 mg higher vs placebo</td>
</tr>
<tr>
<td><strong>Hyperglycaemia with ketosis</strong></td>
<td>Lira 1.8 mg higher vs placebo</td>
<td>Lira 1.8 mg higher vs placebo</td>
</tr>
</tbody>
</table>


Liraglutide is not approved for the management of type 1 diabetes.

---

### Weekly CGM Record for One Patient Prior to Liraglutide

VARANASI A et al. *Eur J Endocrinol* 2011;165:77-84
There are 3 different drugs being studied in type 1 diabetes (empagliflozin, dapagliflozin and sotagliflozin).

Sotagliflozin has filed with the FDA and is the furthest alone in development and will review the clinical trial data for Sotagliflozin in detail and summarize the other studies and also shown in the supplemental slide PDF.

If any are approved it would be the first oral agent for type 1 diabetes.
RENAL HANDLING OF GLUCOSE

(180 L/day) (1000 mg/L) = 180 g/day

GLUCOSE ABSORPTION AND REABSORPTION IN PATIENTS WITH DIABETES TREATED WITH A SELECTIVE SGLT2 INHIBITOR: CANAGLIFLOZIN, DAPAGLIFLOZIN, EMPAGLIFLOZIN, ERTUGLIFLOZIN
GLUCOSE ABSORPTION/REABSORPTION IN PATIENTS TREATED WITH A DUAL SGLT1 & SGLT2 INHIBITOR (SOTAGLIFLOZIN):
INHIBITS SGLT1 LOCALLY IN THE GI TRACT AND SGLT2 SYSTEMICALLY IN THE KIDNEY

INTANDEM STUDY DESIGN

Screening A1C
Baseline A1C
Primary endpoint A1C
Week 52 endpoint A1C
2-Week Screening
2-Week run-in
IDMC review / A1C masked
Insulin optimization
DB core treatment
DB extension
Placebo (n=268)
Sotagliflozin 200 mg (n=263)
Sotagliflozin 400 mg (n=262)

DB, double-blind; R, randomized.
Optimized insulin: Insulin adjustment to meet standard of care (SOC) glycemic targets starting 6-weeks prior to randomization and continued for entire study. An independent Insulin Dose Monitoring Committee (IDMC) assessed SOC adherence and provided feedback to PI if deviations from SOC observed prior to Week 24.
**INTANDEM1: A1C**

- **Screening = 8.2% - 8.3%

- **24-Week Difference from PBO**
  - Sotagliflozin 200 mg: -0.36% (-0.45, -0.27); P<0.001
  - Sotagliflozin 400 mg: -0.41% (-0.50, -0.32); P<0.001

- **52-Week Difference from PBO**
  - Sotagliflozin 200 mg: -0.25% (-0.37, -0.14); P<0.001
  - Sotagliflozin 400 mg: -0.31% (-0.43, -0.20); P<0.001

**Baseline = 7.5% - 7.6%

** INTANDEM1: INSULIN DOSE **

- **Total**
  - Placebo: 66.8
  - Sotagliflozin 200 mg: 65.1
  - Sotagliflozin 400 mg: 64.2

- **Basal**
  - Placebo: 35.1
  - Sotagliflozin 200 mg: 34.8
  - Sotagliflozin 400 mg: 33.4

- **Bolus**
  - Placebo: 31.7
  - Sotagliflozin 200 mg: 30.3
  - Sotagliflozin 400 mg: 30.8

LSTM, least squares mean.
Data presented as the mean change from baseline in insulin dose (95% CI), P-value.
**INTANDEM1: WEIGHT**

Baseline = 87 kg

<table>
<thead>
<tr>
<th>Week Difference from PBO</th>
<th>24-Week Difference from PBO</th>
<th>52-Week Difference from PBO</th>
</tr>
</thead>
<tbody>
<tr>
<td>-2.35 kg (-2.85, -1.85); P&lt;0.001</td>
<td>-3.35 kg (-3.95, -2.94); P&lt;0.001</td>
<td>-3.14 kg (-3.81, -2.46); P&lt;0.001</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Weight, LSM Change from Baseline ± SE (kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
</tr>
<tr>
<td>Sotagliflozin 200 mg</td>
</tr>
<tr>
<td>Sotagliflozin 400 mg</td>
</tr>
</tbody>
</table>

**INTANDEM 1&2 (POOLED): CONTINUOUS GLUCOSE MONITORING**

“TIME IN RANGE” (70-180 MG/DL)

Baseline

| Placebo |
| Sotagliflozin 200 mg |
| Sotagliflozin 400 mg |

Week 24

| <70 mg/dL | 70-180 mg/dL | >180 mg/dL |

Dann T et al. Poster presented at ADA 2018, 1179P
SUMMARIZE FINDINGS FROM ALL SGLT-1/2 INHIBITORS

(DIFFICULT TO MAKE PRECISE EFFICACY COMPARISONS ACROSS TRIALS DUE TO DESIGN AND ANALYSIS DIFFERENCES)

<table>
<thead>
<tr>
<th>Efficacy (placebo adjusted)</th>
<th>Highest dose*</th>
</tr>
</thead>
<tbody>
<tr>
<td>A1C reduction</td>
<td>~0.4%</td>
</tr>
<tr>
<td>Time in Range (blinded CGM)</td>
<td>~3 hour increase</td>
</tr>
<tr>
<td>Time in Hypoglycemia (CGM)</td>
<td>No change or some reduction</td>
</tr>
<tr>
<td>Insulin dose</td>
<td>10-15% reduction</td>
</tr>
<tr>
<td>Weight</td>
<td>~2-3 kg reduction</td>
</tr>
<tr>
<td>Systolic blood pressure</td>
<td>~3-4 mm Hg reduction</td>
</tr>
<tr>
<td>Patient reported outcomes</td>
<td>Improved</td>
</tr>
</tbody>
</table>

Clinically relevant adverse events include genital mycotic infections (primarily in women 12 to 15%) and DKA (3 to 4%), sometimes euglycemic DKA

*R Lower doses retain much of the glycemic efficacy with lesser effect on weight and blood pressure

RISK MITIGATION OF DKA WITH SGLT INHIBITORS

- Hold the SGLT inhibitor
  - when NPO is required, viral illness, surgery, colonoscopy, etc.
- Avoid the keto diets and and excess alcohol
- Do not prescribe in poorly adherent patients and use with caution if A1c above 9% or frequent episodes of DKA
- If nauseous or sick in any way, hold the SGLT inhibitor and troubleshoot their insulin delivery and check blood or urine ketones. If ketones are positive, take insulin per protocol along with carbs and fluids (your glucose may be normal!)
- If unable to drink and eat, go to the ER for fluids and further management.
APPROACH TO REDUCE DKA RISK WITH SGLTIS: STICH PROTOCOL

Wallet Card - front

ST
STop SGLT inhibitor

I
inject bolus Insulin

C
consume 30 g Carbohydrates

H
Hydrate (drink water)

Please carry this card if you are using a SGLT inhibitor with insulin to treat diabetes.


AN ARTIFICIAL PANCREAS IS COMING FASTER THAN WE THOUGHT POSSIBLE

iLet • BigFoot • Tandem • Insulet • Lilly • Medtronic

BG mg/dL

180

Alarm – impending hypo

No response – alarm plus insulin reduction or off/glucagon on if needed

Alarm – impending hyper

No response – alarm plus automated insulin push to bring level below threshold (glucagon off)

Resume preset basal rate

Minimize time in “Red” zones

Time

Type 1 New and Emerging CME
Enduring Webcast 2019
The important unmet needs in T1D include improved glycemic variability (GV), increased time in range (TIR)

Reaching A1c goal without hypoglycemia

Controlling blood pressure and weight gain

Addressing the emotional burden of living

CGM and the newer ultra rapid and basal insulins can help improve TIR

Adjunctive therapies can address some of the unmet needs