LIRAGLUTIDE IN TYPE 1 DIABETES MELLITUS

HAITHAM HASSANE, MD

Mentor: Nitesh Kuhadiya, MD, MPH
Objective

• To determine if addition of liraglutide to insulin in T1DM leads to improvement in glycemic control.
• To determine the durability of results over 26 weeks.
Background

• Control of glucose homeostasis in patients with type 1 diabetes has proven to be difficult, as:-
  • Exogenous insulin does not compensate for bioavailability.
  • Postprandial increase of glucagon is uninhibited.

• Newer agents like liraglutide (Glucagon-like Peptide-1) have multiple mechanisms of action. They have an established use in T2DM, but not in T1DM.
Liraglutide: Mechanism of Action

Liver
- Helps lower hepatic glucose output by suppressing pancreatic glucagon secretion.

Gut
- Slows gastric emptying and the rate at which glucose enters the blood after meals.

Pancreas
- Stimulates beta cells to release insulin when blood glucose is high.
Previous Studies: Liraglutide in T1DM

1. **2013**: Addition of liraglutide to insulin in *obese* patients with T1DM led to improvements in HbA1c and to reductions in insulin dose, systolic blood pressure, and body weight.

2. **2016**: Addition of liraglutide to insulin over a 12-week period in overweight and *obese* patients with T1DM resulted in modest reductions of weekly mean glucose levels with significant weight loss and small insulin dose reductions.


Hypothesis

• Liraglutide in patients with type 1 diabetes
  • ↓ HbA1c, fasting, postprandial and the overall mean glucose concentrations
  • ↓ insulin dose required

• Will compare the following among liraglutide versus placebo groups:
  • HbA1c
  • Mean fasting glucose & mean weekly glucose (and their standard deviations)
  • Insulin dose required
METHODS: Study Design

• Prospective, randomized, double-blinded, placebo controlled study for the first 26 weeks.

• Placebo patients crossed over at week 26. Open label study for the next 26 weeks.

• To avoid hypoglycemia/nausea, patients started on 0.6 mg liraglutide per day; titrated up to 1.2 mg, then 1.8 mg over 4-5 weeks based on tolerability.

• Conducted at the Diabetes Endocrinology Center of WNY (SUNY at Buffalo).

• Funded by the National Institute of Health (NIH).
METHODS: Study Population

• Target size is 96 T1DM patients on insulin pump or multiple injections of insulin per day.

• Randomized to 2 groups:
  • placebo vs 1.8 mg liraglutide daily
METHODS: Outcome Measures

Primary endpoint

• Detect a difference in HbA1c after 26 weeks of treatment with Liraglutide or placebo.

Secondary endpoint

• Detect a difference between the 2 groups in:
  • mean weekly blood glucose concentrations
  • mean fasting blood glucose concentrations
  • insulin dose
METHODS: Inclusion Criteria

1. Type 1 Diabetes on continuous subcutaneous insulin infusion (CSII; also known as insulin pump) or multiple (4 or more) injections of insulin per day.
2. Regularly measuring blood sugars four times daily.
3. HbA1c <8.5%.
4. Well versed with carbohydrate counting.
5. Age 18-75 years.
6. BMI 20-40 kg/m².
METHODS: Exclusion criteria

1. Type 1 diabetes <6 months.
2. Coronary event or procedure (myocardial infarction, unstable angina, coronary artery bypass, surgery or coronary angioplasty) in the previous four weeks.
3. Hepatic disease (transaminase > 3 times normal) or cirrhosis.
4. Renal impairment (serum eGFR<30ml/min/1.73m²).
5. HIV or Hepatitis B or C positive status.
6. Participation in any other concurrent clinical trial.
7. Inability to give informed consent.
8. Any other life-threatening, non-cardiac disease.
9. Use of an investigational agent or therapeutic regimen within 30 days of study.
11. History of gastroparesis.
12. **History of pancreatitis.**
13. **History of medullary thyroid carcinoma or MEN 2 syndrome.**
METHODS: Screening & Randomization

• Screening day
  • History & physical exam.
  • Informed consent.
  • Fasting baseline labs - CBC, CMP, HbA1c.

• Randomization method
  • Subjects who meet criteria are assigned a random number using Microsoft Excel.
## Baseline Characteristics (± SD)

<table>
<thead>
<tr>
<th>Index</th>
<th>Placebo (n=10)</th>
<th>Liraglutide (n=19)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>49 ± 13.73</td>
<td>51 ± 14.03</td>
<td>0.91</td>
</tr>
<tr>
<td>Age of T1D on diagnosis</td>
<td>20.5 ± 9.52</td>
<td>30.1 ± 11.82</td>
<td>0.04</td>
</tr>
<tr>
<td>HbA1c</td>
<td>7.5 ± 0.7</td>
<td>8 ± 0.9</td>
<td>0.14</td>
</tr>
<tr>
<td>Weight</td>
<td>159.3 ± 60.5</td>
<td>166 ± 46.6</td>
<td>0.97</td>
</tr>
<tr>
<td>BMI</td>
<td>28 ± 11.29</td>
<td>26.8 ± 5.1</td>
<td>0.42</td>
</tr>
<tr>
<td>Weekly mean glucose</td>
<td>173 ± 27.1</td>
<td>179.2 ± 27.2</td>
<td>0.57</td>
</tr>
<tr>
<td>Weekly mean fasting</td>
<td>155.5 ± 33</td>
<td>172.9 ± 42.6</td>
<td>0.24</td>
</tr>
<tr>
<td>Weekly basal insulin</td>
<td>27.7 ± 13.9</td>
<td>24 ± 8.4</td>
<td>0.45</td>
</tr>
<tr>
<td>Weekly bolus insulin</td>
<td>26.8 ± 14.7</td>
<td>23.5 ± 11.8</td>
<td>0.54</td>
</tr>
<tr>
<td>Weekly total insulin</td>
<td>54.6 ± 25.1</td>
<td>47.8 ± 17.9</td>
<td>0.46</td>
</tr>
<tr>
<td>Weekly carb intake (gm)</td>
<td>162.2 ± 76</td>
<td>169.3 ± 73.2</td>
<td>0.81</td>
</tr>
<tr>
<td>SBP</td>
<td>128 ± 7.9</td>
<td>127.1 ± 13</td>
<td>0.88</td>
</tr>
<tr>
<td>DBP</td>
<td>77.2 ± 9</td>
<td>77.3 ± 12.4</td>
<td>0.98</td>
</tr>
</tbody>
</table>
# Flow Chart of Study Procedures

<table>
<thead>
<tr>
<th>VISIT</th>
<th>History &amp; Physical Exam</th>
<th>HbA1c</th>
<th>Dietician</th>
<th>Collect Fingerstick/CGM Data &amp; Adjust Insulin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Screening</td>
<td>x</td>
<td>x</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Day -30</td>
<td></td>
<td>x</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Day -20, -10</td>
<td></td>
<td></td>
<td>x</td>
<td></td>
</tr>
<tr>
<td>Day 0</td>
<td></td>
<td></td>
<td>x</td>
<td></td>
</tr>
<tr>
<td>Day 10, 20, 30</td>
<td></td>
<td></td>
<td>x</td>
<td></td>
</tr>
<tr>
<td>Week 12</td>
<td>x</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Week 8, 16, 20</td>
<td></td>
<td></td>
<td>x</td>
<td></td>
</tr>
<tr>
<td>Week 24</td>
<td></td>
<td></td>
<td>x</td>
<td></td>
</tr>
<tr>
<td><strong>Week 26</strong> CROSS-OVER</td>
<td>x</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Week 27 (Cross-over group only)</td>
<td></td>
<td></td>
<td>x</td>
<td></td>
</tr>
<tr>
<td>Week 28</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Week 29 (Cross-over group only)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Week 32, 36</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Week 40</td>
<td>x</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Week 44</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Week 48</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Week 52</td>
<td>x</td>
<td>x</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Current Data

• Recruited 64 patients (32 drug, 32 placebo).
• Complete data unblinded (19 drug, 10 placebo).
• 2-tailed, unpaired t-test:-
  • compared mean values of various indices between placebo & liraglutide groups at day/week 0, week 26, and week 52.
  • compared delta change averages of various indices between placebo & liraglutide groups.
RESULTS: Mean HbA1c (%)
**RESULTS:** Time Spent at Week 26

![Pie chart showing the time spent at different glucose levels for Placebo Group.]

- <55 mg/dL: 34%
- ≥55-<70 mg/dL: 3%
- ≥70-≤160 mg/dL: 15%
- >160-≤240 mg/dL: 42%
- >240 mg/dL: 6%
RESULTS: Time Spent at Week 26

Liraglutide Group

- <55 mg/dL: 20%
- 55-<70 mg/dL: 4%
- ≥70-≤160 mg/dL: 33%
- >160-≤240 mg/dL: 37%
- >240 mg/dL: 6%
**RESULTS:** Time Spent at Week 26

<table>
<thead>
<tr>
<th>Glucose Range</th>
<th>Placebo (± SD)</th>
<th>Liraglutide (± SD)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;55 mg/dL</td>
<td>3% ± 3.70</td>
<td>4% ± 5.47</td>
<td>0.93</td>
</tr>
<tr>
<td>≥55-&lt;70 mg/dL</td>
<td>6% ± 3.44</td>
<td>6% ± 5.57</td>
<td>0.76</td>
</tr>
<tr>
<td>≥70-≤160 mg/dL</td>
<td>42% ± 20.82</td>
<td>37% ± 13.52</td>
<td>0.36</td>
</tr>
<tr>
<td>&gt;160-≤240 mg/dL</td>
<td>34% ± 14.36</td>
<td>33% ± 10.24</td>
<td>0.12</td>
</tr>
<tr>
<td>&gt;240 mg/dL</td>
<td>15% ± 6.53</td>
<td>20% ± 11.64</td>
<td>0.58</td>
</tr>
</tbody>
</table>
RESULTS: Mean Weekly Glucose (mg/dL)
RESULTS: Mean Weekly Fasting Glucose (mg/dL)

- Placebo (switched to Liraglutide at week 26)
- Liraglutide

Day 0: Placebo 156.3, Liraglutide 152.2
Week 26: Placebo 165.1, Liraglutide 153.9
Week 52: Placebo 153.6, Liraglutide 137.8

P=0.56 (Δ)
RESULTS: Mean Weekly Basal Insulin (unit)

P = 0.21 (Δ)
RESULTS: Mean Weekly Bolus Insulin (unit)

P = 0.93 (∆)
RESULTS: Mean Weekly Total Insulin (unit)

P = 0.81 (Δ)

Legend:
- Placebo (switched to Liraglutide at week 26)
- Liraglutide
RESULTS: Mean Weekly Carbohydrate Intake (gm)

- Placebo (switched to Liraglutide at week 26)
- Liraglutide

P = 0.90 (Δ)
RESULTS: Mean Weight (lb)

P = 0.06 (Δ)
RESULTS: Mean Systolic Blood Pressure (mmHg)

P = 0.04 (Δ)
## COMPARISON OF AVERAGE DELTA CHANGES AMONG PLACEBO VERSUS LIRAGLUTIDE GROUPS

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Change over 26 weeks (± SD)</th>
<th>Change over 52 weeks (± SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Placebo (n=10)</td>
<td>Liraglutide (n=19)</td>
</tr>
<tr>
<td>HbA1c (%)</td>
<td>0.2 ± 0.5</td>
<td>-0.4 ± 0.7</td>
</tr>
<tr>
<td>Average Weekly Glucose (mg/dL)</td>
<td>0.9 ± 23.5</td>
<td>-8.3 ± 26.8</td>
</tr>
<tr>
<td>Fasting Weekly glucose (mg/dL)</td>
<td>12.9 ± 67.0</td>
<td>-2.9 ± 55.6</td>
</tr>
<tr>
<td>Standard Deviation (SD)</td>
<td>2.6 ± 16.5</td>
<td>-6.2 ± 12.9</td>
</tr>
<tr>
<td>Body Weight (lb)</td>
<td>-3.4 ± 4.2</td>
<td>-7.6 ± 7.5</td>
</tr>
<tr>
<td>Weekly Total Insulin dose (unit)</td>
<td>-1.5 ± 6.7</td>
<td>-2.2 ± 7.8</td>
</tr>
<tr>
<td>Weekly Total Insulin dose SD (unit)</td>
<td>-1.2 ± 4.1</td>
<td>-0.3 ± 3.6</td>
</tr>
<tr>
<td>Basal Insulin Dose (unit)</td>
<td>1.3 ± 1.9</td>
<td>-0.2 ± 4.6</td>
</tr>
<tr>
<td>Basal SD (unit)</td>
<td>-0.5 ± 1.2</td>
<td>-0.9 ± 2.5</td>
</tr>
<tr>
<td>Weekly Bolus Insulin Dose (unit)</td>
<td>-2.3 ± 7.9</td>
<td>-2.0 ± 5.1</td>
</tr>
<tr>
<td>Weekly Bolus SD (unit)</td>
<td>-1.1 ± 3.8</td>
<td>-1.0 ± 3.8</td>
</tr>
</tbody>
</table>
## COMPARISON OF AVERAGE DELTA CHANGES AMONG PLACEBO VERSUS LIRAGlutide GROUPS

**CONTD.**

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Change over 26 weeks (± SD)</th>
<th>Change over 52 weeks (± SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Placebo (n=10)</td>
<td>Lirag. (n=19)</td>
</tr>
<tr>
<td>Weekly Carb Intake (gm)</td>
<td>-16.4 ± 64.7</td>
<td>-13.8 ± 40.1</td>
</tr>
<tr>
<td>Weekly Carb Intake SD</td>
<td>-4.5 ± 13.3</td>
<td>-1.0 ± 20.6</td>
</tr>
<tr>
<td>Weekly Carb Entries</td>
<td>-0.3 ± 1.6</td>
<td>-0.1 ± 0.8</td>
</tr>
<tr>
<td><strong>SBP (mmHg)</strong></td>
<td><strong>7.7 ± 13.1</strong></td>
<td><strong>-10.4 ± 33.1</strong></td>
</tr>
<tr>
<td><strong>DBP (mmHg)</strong></td>
<td><strong>4.4 ± 9.6</strong></td>
<td><strong>-0.6 ± 6.4</strong></td>
</tr>
</tbody>
</table>
Summary of Results

• In the liraglutide group vs placebo, statistically significant ↓ in:
  • HbA1c (at week 26) – primary endpoint achieved
  • Systolic blood pressure (at week 26)

• Statistically insignificant ↓ in:
  • Average and fasting weekly glucose
  • Body weight
  • Insulin requirements
  • Diastolic blood pressure

• Statistically insignificant change in time spent in eu/hypo/hyperglycemia.
Discussion

• Most patients included were not obese (mean BMI=26.8-28), so this may explain why weight loss is not statistically significant.

• ↓ systolic blood pressure despite non-significant change in weight – due to ↑ arterial compliance and ↓ arterial stiffness. [3]
  
  • Stimulation of endothelial nitric oxide synthase (eNOS) and ↑ nitric oxide release has been described. [4][5]

Conclusion

• *Liraglutide* improved glycemic control in **non-obese** T1DM patients.

• It decreased **systolic blood pressure**.

• Effects on weight loss may **not** be as profound in non-obese T1DM patients (compared to studies that included obese patients).

• Study is ongoing, and a larger sample may yield more statistically significant results.
Thanks

• Dr. Nitesh Kuhadiya
• Dr. Husam Ghanim
• Dr. Henri Woodman
• Dr. M. Umer Butt