Welcome to UVM ECHO:
Treatment of Diabetes Mellitus Type II

Facilitators: Mark Pasanen MD
Liz Cote
November 12, 2020
“Introduction” to ZOOM

- Please mute microphone when not speaking
- Please use camera as much as possible
- Test both audio & video before joining
- Communicate clearly during clinic:
  - Can use “raise hand” feature to comment
  - Speak clearly
  - Use chat function for technical issues
- We are recording the didactic section
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Disclosures: None or have been resolved

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• Joel Schnure, MD
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Diabetes Echo 11/12/2020
Beyond Basal Insulin Therapy

Jack L. Leahy, M.D.
Endocrinology, Diabetes and Metabolism
University of Vermont
ADA/EASD Guidelines for Starting Insulin Therapy in Type 2 DM

Use Principles in Figure 9.1, including reinforcement of behavioral interventions (weight management and physical activity) and provision of DSMES to meet individualized treatment goals.

If injectable therapy is needed to reduce A1C

Consider GLP-1 RA in most patients prior to insulin

INITIATION: Initiate appropriate starting dose for agent selected (varies within class)
TITRATION: Gradual titration to maintenance dose (varies within class)

If above A1C target

Add basal insulin

Choice of basal insulin should be based on patient-specific considerations, including cost. Refer to Table 9.3 for insulin cost information.

Add basal analog or bedtime NPH insulin

INITIATION: Start 10 IU a day OR 0.1-0.2 IU/kg a day
TITRATION:
- Set FPG target (see Section 6: Glycemic Targets)
- Choose evidence-based titration algorithm, e.g., increase 2 units every 3 days to reach FPG target without hypoglycemia
- For hypoglycemia determine cause, if no clear reason lower does by 10-20%

If on GLP-1 RA or if GLP-1 RA not appropriate or insulin preferred

Why GLP-1 RA vs Basal Insulin?
Available GLP-1 RA Agents in the US

GLP-1 RA

Short-acting (<24 hours)
- Exenatide BID
  - Byetta
- Lixisenatide Daily
  - Adlyxin

Long-acting (≥24 hours)
- Liraglutide Daily
  - Victoza
- Exenatide Weekly
  - Bydureon
- Dulaglutide Weekly
  - Trulicity
- Semaglutide Weekly
  - Ozempic
- Oral Semaglutide
  - Rybelsus
<table>
<thead>
<tr>
<th>Comparison GLP-1 RA Agents and Insulin</th>
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</thead>
<tbody>
<tr>
<td><strong>Actions</strong></td>
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<tr>
<td>-----------</td>
</tr>
<tr>
<td>Actions</td>
</tr>
<tr>
<td>Weight</td>
</tr>
<tr>
<td>Hypoglycemia</td>
</tr>
<tr>
<td>Injections</td>
</tr>
<tr>
<td>Require titration</td>
</tr>
<tr>
<td>GI side effects</td>
</tr>
<tr>
<td>CV protection</td>
</tr>
<tr>
<td>Renal protection</td>
</tr>
</tbody>
</table>
SET IT AND FORGET IT
Liraglutide vs. Once-Daily Insulin Glargine
26-weeks. Baseline A1c 8.2%. N = 549

Weight change (kg)
- LIRA 1.8 mg once daily: -1.8
- Insulin glargine: 1.6

Major hypoglycemia (events/patient-year)
- LIRA: 0.06
- Insulin glargine: 0.0

Minor hypoglycemia (events/patient-year)
- LIRA: 1.2
- Insulin glargine: 1.3

P < 0.05

Failing Oral Therapy: Efficacy of GLP-1 RAs Compared to Basal Insulin

Average weight change: GLP-1 RA -1.8 to -2.7 kg versus insulin +1.4 to +3.0 kg

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**Δ A1C, % from BL**

- **EXN BID**: MET + SU -1.1, MET ± SU -0.8
- **ALBI**: MET + SU -1.1, MET ± SU -0.7
- **LIRA**: MET + SU -1.1, MET ± SU -0.9
- **EXN QW**: MET + GLIM -1.1, MET ± SU -1.3
- **DULA**: MET + GLIM -1.1
- **GLAR**: MET ± SU -0.9
- **DET**: MET + GLIM -0.6

**Noninferior vs insulin**

- **1,a**: 26 weeks, BL A1C 8.2% to 8.7%.
- **2,b**: 52 weeks, BL A1C 8.3%, 82% on MET + SU background.
- **3,a**: ≈ 70% on MET + SU background.
- **4,a,c**: 52 weeks, BL A1C 8.1%.
- **5,d**: 52 weeks, BL A1C 8.1%.

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Combination of Basal Insulin With a GLP-1 Receptor Agonists Has Scientific Logic

Basal insulin analogs
- Simple to initiate
- Control nocturnal and FPG
- Lower hypoglycemia risk vs. NPH
- Modest weight increase (1–3 kg)
- Achieve A1C targets in ~50%–60%
- Lower doses need with GLP-1 RA use

GLP-1 RAs
- Simple to initiate
- Pronounced PPG control (fewer injections than meal-time insulin)
- Low risk for hypoglycemia
- Weight-lowering effects
- Achieve A1C targets in ~40%–60%
- Coformulations with insulin under investigation

DUAL I – Comparison IDegLira Versus the Individual Agents in Insulin Näive

- 26 week open label comparison of fixed dose insulin degludec + liraglutide (n=834) to insulin degludec (414) or liraglutide (415).
- Patients: on metformin ± pioglitazone, A1c 8.3%

<table>
<thead>
<tr>
<th></th>
<th>IDegLira</th>
<th>Degludec</th>
<th>Liraglutide</th>
</tr>
</thead>
<tbody>
<tr>
<td>Final A1c</td>
<td>6.4%</td>
<td>6.9%</td>
<td>7.0%</td>
</tr>
<tr>
<td></td>
<td>Noninferior Degludec Superior to Liraglutide</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>8.8%</td>
<td>3.6%</td>
<td>19.7%</td>
</tr>
<tr>
<td>Weight</td>
<td>-0.5 kg</td>
<td>1.6 kg</td>
<td>-3.0 kg</td>
</tr>
</tbody>
</table>

LixiLan-O – Comparison LixiLan Versus the Individual Agents in OHA Failures

• 26 week open label comparison of fixed dose insulin glargine + lixisenatide to insulin degludec or liraglutide (total 1,170).
• Patients: on metformin ± second OHA, A1c 8.1%

<table>
<thead>
<tr>
<th></th>
<th>LixiLan</th>
<th>Glargine</th>
<th>Lixisenatide</th>
</tr>
</thead>
<tbody>
<tr>
<td>Final A1c</td>
<td>6.5%</td>
<td>6.8%</td>
<td>7.3%</td>
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<tr>
<td></td>
<td>Superior both Glargine and Lixisenatide</td>
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<tr>
<td>BG &lt;70 mg/dL</td>
<td>1.4/pt-year</td>
<td>1.2/pt-year</td>
<td>0.3/pt-year</td>
</tr>
<tr>
<td>Weight</td>
<td>-0.3 kg</td>
<td>1.1 kg</td>
<td>-2.3 kg</td>
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What if Basal Insulin is Not Enough?
After First Injection ADA/EASD Guidelines in Type 2 DM

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Stepwise Treatment of Type 2 Diabetes

- **Lifestyle changes + Metformin**
- **Additional Oral agents**
- **Basal**: Add basal insulin and titrate
- **Basal Plus**: Add prandial insulin at main meal
- **Basal Bolus**: Further intensification

Progressive deterioration of β-cell function
<table>
<thead>
<tr>
<th></th>
<th>BREAKFAST</th>
<th>LUNCH</th>
<th>DINNER</th>
<th>HS</th>
<th>Middle of night</th>
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<tr>
<td>Monday</td>
<td>107</td>
<td>126</td>
<td>133</td>
<td>185</td>
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<td>Saturday</td>
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<td>Sunday</td>
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</table>
All-to-Target: Stepwise Intensification With Glargine and Glulisine vs Aspart Premix

- 60-week study of 3 treatment strategies in 572 patients on orals with average A1c 9.4%.
  - Optimize glargine followed adding 1 injection glulisine (Basal plus)
  - Optimize glargine followed by stepped addition to 3 injections glulisine (Basal bolus)
  - Twice daily aspart 70/30 (Premix).
- 49% reached A1c <7% with basal plus versus 39% with premix (p<0.05)
- 40-60% reduction in hypoglycemia with basal plus versus premix (P<0.01)

Mealtime Insulin

- Use rapid-acting analogues, not regular insulin
  - Less postprandial hypoglycemia
  - Can be taken up to 20 minutes after start eating
  - Best about 15 minutes premeal.

- Start with 1 shot, at largest meal:
  - 4 units, and titrate, OR
  - By weight - 0.1 U/kg

- Titrate to:
  - <160 mg/dL 2 hours post-prandial OR
  - <130 mg/dL next meal or bedtime

- Carb counting in type 2 DM – unproven.

Leahy JL. *Endocrinol Metab Clin North Am* 2012;41:119-144
What About Agents Other Than Prandial Insulin?
Addition of Twice-daily Exenatide to Glargine Insulin-treated Type 2 DM

- N=259. Baseline A1c 8.5% (placebo) and 8.32% (exenatide)
- Better improvement A1c: -1.7% exenatide versus -1.0% placebo.
- Weight loss: -1.8 kg with exenatide versus +1.0 kg placebo.
- Smaller increase glargine dose: 13 units exenatide versus 20 placebo.
- Similar hypoglycemia.
- More study dropouts: 13 exenatide versus 1 placebo
GLP-1 RA vs Prandial insulin Added to Basal Insulin

<table>
<thead>
<tr>
<th>Outcome</th>
<th>LIRA vs ASP$^1$</th>
<th>EXN BID vs LIS$^2$</th>
<th>ALBI vs LIS$^3$</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\Delta$ Weight, kg</td>
<td>$-2.8$</td>
<td>0.9</td>
<td>$-2.5$</td>
</tr>
<tr>
<td>Hypo, EPYe</td>
<td>1.0</td>
<td>8.2</td>
<td>2.1</td>
</tr>
<tr>
<td>Nausea, %</td>
<td>LIRA &gt; ASP, first 2 wk</td>
<td>2.9</td>
<td>0</td>
</tr>
</tbody>
</table>

DPP-4 Inhibitors Added to Regimens That Include Insulin

Baseline A1c (%)

SGLT2 Inhibitors Added to Regimens That Include Insulin

a SGLT2is are not approved for weight loss; data are from individual trials and do not represent head-to-head comparisons: 18-24 weeks; BL A1C, 8.3%-8.6%; BL weight, 95-97 kg.
b CANA added to basal, bolus, or basal/bolus insulin; ≥ 30 U/d with or without other AHAs.
c DAPA added to unspecified stable insulin regimen; ≥ 30 U/d and ≤ 2 other AHAs.
d EMPA added to basal insulin (45-48 U/d) with or without MET and/or SU.
Conclusions

• Injection therapy (GLP-1 RA or basal insulin) has higher potency than oral pharmaceuticals in type 2 DM.
• Can start with either although very different clinical profiles.
• Diabetes specialty world recommends GLP-1 RA agents as first agent if affordable and tolerated – high potency, weekly, easy titration, weight loss, low rate of hypoglycemia, CVD/renal benefits.
• Next steps after basal insulin:
  - Prandial insulin – often start with single injection largest meal.
  - GLP-1 RA therapy.
  - Other agents (A1c < mid 7s).
• RECORDING TO BE STOPPED FOR CASE PRESENTATION
The discussion and materials included in this conference are confidential and privileged pursuant to 26VSA Section 1441-1443. This material is intended for use in improving patient care. It is privileged and strictly confidential and is to be used only for the evaluation and improvement of patient care.
ECHO Reminders

• Volunteers to present cases (this is key to the Project ECHO model)
• Please complete evaluation survey for each session
  • CME code will be emailed once session evaluation form is received at UVM
• UVM Project ECHO materials available at www.vtahec.org
• Please contact us with any questions/suggestions
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