Incorporating GLP-1 Receptor Agonist Therapy in T2DM Management: Achieving a Comfort Zone in 2014

February 6, 2014
Fort Lauderdale, FL

Educational Partner
Session 3: Incorporating GLP-1 Receptor Agonist Therapy in T2DM Management: Achieving a Comfort Zone in 2014

Learning Objectives

1. Implement treatment regimens for patients with type 2 diabetes in accordance with recently updated treatment recommendations
2. Review the clinical evidence for the use of incretin-based therapies in type 2 diabetes management

Faculty
Jack L. Leahy, MD
Professor of Medicine
Chief, Division of Endocrinology, Diabetes and Metabolism
University of Vermont
Burlington, Vermont

Dr Jack Leahy is a professor in the department of medicine and codirector of the division of endocrinology, diabetes and metabolism at the University of Vermont. After receiving his BS from the University of Toronto and his MD from the Medical College of Virginia, Dr Leahy completed his medical and endocrine training at the Medical College of Virginia and then joined the faculty of Harvard Medical School in 1984 and Tufts University School of Medicine in 1992. He has been at the University of Vermont since 1996, where his primary clinical interest is diabetes. He also runs a basic research laboratory that is focused on identifying the molecular mechanisms behind the islet beta cell failure in type 2 diabetes. He has published more than 90 articles and chapters on the pathogenesis and management of the disease.

Javier Morales, MD
St. Francis Hospital
Vice President
Principal Clinical Trials Investigator
Advanced Internal Medicine Group, PC
Great Neck, New York

Dr Javier Morales is in private practice with the Advanced Internal Medicine Group, Great Neck, New York. After graduating from the University of Medicine and Dentistry of New Jersey (UMDNJ)-New Jersey Medical School, he continued his medical training with residencies at Memorial Sloan-Kettering Cancer Center and North Shore University Hospital; where he served as chief medical resident. He sits on multiple committees at St. Francis Hospital, Roslyn, New York, has contributed to several publications, and has served as principal investigator for numerous studies and clinical trials. He is also clinical instructor for several nurse practitioner and physician assistant programs in addition to the internal medicine residency program at North Shore University Hospital and Winthrop University Hospital.

Jeff Unger, MD
American Board of Family Medicine
Director, Metabolic Studies
Catalina Research Institute
Chino, California

Dr Jeff Unger is the current director of metabolic studies at the Catalina Research Institute, Chino, California. The research center incorporates primary care with clinical research in areas related to diabetes, sexual dysfunction, diabetic neuropathy, diabetic nephropathy, hyperlipidemia, hypertension, pain, obesity and mental illness.

A board certified family physician and a fellow of the American Association of Clinical Endocrinologists, Dr Unger is an international primary care thought leader in the field of diabetes. He has educated patients and clinicians around the world regarding intensive diabetes management through both speeches and his textbook “Diabetes Management in Primary Care.” An avid writer, Dr Unger has published more than 160 peer reviewed articles on headaches and diabetes. He also serves on the editorial boards of several medical journals.
Faculty Financial Disclosure Statements
The presenting faculty reported the following:

Jack L. Leahy, MD, serves as an advisor for Merck, Novo Nordisk, Sanofi.

Javier Morales, MD, serves as an advisor for BI, Bristol Myers Squibb, Novo Nordisk, Pfizer, Sanofi-Aventis and Warner Chilcott; and participates in speakers bureau for Novo Nordisk, Sanofi-Aventis and Warner Chilcott.

Jeff Unger, MD, participates in speakers bureau for Janssen Pharmaceuticals, Novo Nordisk and Valeritas. Serves as an advisor or consultant for Dance Pharmaceuticals, Halozyme, Johnson and Johnson, Novo Nordisk, Sanofi-Aventis and Valeritas; receives grants for clinical research from BI, GSK, Johnson and Johnson, Lilly, Novo Nordisk, Pfizer and Sanofi-Aventis; and receives payment for clinical trials program from Catalina Research Institute.

Education Partner Financial Disclosure Statement
The content collaborators at Vindico Medical Education have reported the following:

Ronald A. Codario, MD, FACP, RPVI, FNLA, CCMEP, Medical Director, has no relevant financial relationships to disclose.

Chris Rosenberg, Director of Medical Education, has no relevant financial relationships to disclose.

Suggested Reading List
Incorporating GLP-1 Receptor Agonist Therapy in T2DM Management: Achieving a Comfort Zone in 2014

SPEAKERS
Jack L. Leahy, MD
Javier Morales, MD
Jeff Unger, MD

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Incorporating GLP-1 Receptor Agonist Therapy in T2DM Management: Achieving a Comfort Zone in 2014

Drug List

Acarbose
Alogliptin
Bromocriptine QR
Colesevelam
Exenatide
Exenatide ER
Exenatide LAR/QW
Glimepiride
Insulin Detemir
Insulin Glargine
Linagliptin
Liraglutide
Losartan
Mellzyme
Orilase
Saxagliptin
Sitagliptin
Vildagliptin

Learning Objectives

• Implement treatment regimens for patients with type 2 diabetes in accordance with recently updated treatment recommendations
• Review the clinical evidence for the use of incretin-based therapies in type 2 diabetes management
Safe, Timely, and Effective Use of Guidelines For Treating Primary Care Patients To Their Metabolic Targets

Jeff Unger, MD, FACE
Medical Director
Unger Primary Care Private Medicine

Why Bother Attending Yet Another Diabetes Lecture?

- 26 million Americans have diabetes and an additional 79 million Americans have prediabetes resulting in $299 billion in healthcare expenditures
- By 2030, over 55 million Americans will have diabetes
- In 2050, 1 in 3 adults will have T2DM
- 90% of all diabetes management occurs within the primary care setting

America is Changing!

Every Single Day in the United States....

- 5,205 new cases of diabetes are diagnosed
- 230 people have a diabetes-related amputation
- 133 people with diabetes progress to end-stage renal disease
- 55 people with diabetes become blind

The Good News In Diabetes Trending!

- Incidence of ESRD over 25 years in patients diagnosed with T1DM from 1970-1980 has been reduced by 70% compared with patients diagnosed from 1922-1969.
- Considering the anticipated tripling of the number of people worldwide to develop T2DM by 2040, only 10% of at risk patients are predicted to develop vision threatening diabetic retinopathy over a 6 year observation period.

One-third of Adults with Diabetes are Undiagnosed

- ~8.3% of US adults have diabetes
- ~26 million persons in 2005
- Nearly one-third of US adults 20 years & older don’t know they have diabetes
- 26% of US adults have impaired fasting glucose (IFG)*

Total: 35% of US adults with undiagnosed diabetes or prediabetes ~79 million persons

Relationship Between BMI and Risk of Type 2 Diabetes

Weight Loss Reduces Cardiometabolic Risk Factors in Patients With Type 2 Diabetes

The Ominous Octet- Its NOT just about “The Sugar!”

Setting Glycemic Targets for Patients With T2DM: ADA/EASD Position Statement Recommendations

Setting Glycemic Targets for Patients with T2DM: AACE Guidelines

AACE/ACE Algorithm for Glycemic Control
Where to Initiate Incretin-Based Therapies

Important Distinctions

1. GLP-1 RA – slow gastric emptying, increase satiety, promote weight reduction, improve cardiovascular risk factors, may improve beta cell mass and function (animal models only), now listed in new AACE guidelines as a treatment option in patients with pre-diabetes (presently off-label)
2. DDP-IV inhibitors – weight neutral, taken orally, generally well tolerated


How to Initiate GLP-1 Agonist Therapy

1. Liraglutide – once daily initially 0.6 mg/day for one week and then 1.2 mg/day. May increase to 1.8 mg daily.
2. If 3 days have elapsed since last dose, reintiate at 0.6 mg/day and the titrate
3. Exenatide – initially 5 mcg twice daily within 60 minutes of AM or PM meals; may increase to 10 mcg twice daily after one month
4. Exenatide extended release – 2 mg once every 7 days

Conclusion

- Multiple defects result in fasting and post-prandial hyperglycemia in type 2 diabetes
- These multiple defects, as well as FPG and PPG, are appropriate targets for therapy directed at attaining A1C goals
- Customized metabolic targets are advisable in all patients. Blood pressure, lipids and glycemia should all be customized.
- Treat as early as possible, as low as possible, as safely as possible, for as long as possible and as rationally as possible. Avoid hypoglycemia!

Revisiting the Mechanism of Action Behind Incretin-based Therapy

Jack L. Leahy, MD
Endocrinology, Diabetes and Metabolism
University of Vermont
USA

Incretins

- Gut-derived hormones:
  - Secreted in response to nutrients, that potentiate insulin secretion and suppress glucagon secretion
  - Act in a glucose-dependent fashion.
  - Signal between food ingestion and postmeal glucose and lipid control.
- Two predominant incretins:
  - Glucagon-like peptide-1 (GLP-1)
  - Glucose-dependent insulinotropic peptide (GIP)
- Rapidly inactivated by dipeptidyl peptidase 4 (DPP-4)
- Incretin effect is impaired in type 2 diabetes mellitus

nutrapeutics. 2004;32:197-204.

GLP-1

GIP

Increased insulin
Lowered glucagon

Enhanced insulin sensitivity

Slowed motility

Increased CV dynamics

Satiety

Anabolic
CV Effects of GLP-1 Receptor Activation

- Improved weight, systolic blood pressure, lipids
- Improved endothelial function
- Increased vasorelaxation
- Increased peripheral and coronary flow
- Increased ventricular function
- Decreased microvascular permeability
- ? Protection against anoxic myocardial damage

Effects in isolated vessels/hearts and GLP-1R expression in CV tissues indicate some effects may be direct.

Treatment Strategies Involving the Incretin System

- DPP-4 enzyme inhibitor:
  - Oral. molecule selectivity inhibits activity of DPP-4.
  - Sitagliptin, saxagliptin, linagliptin, alogliptin in United States.
  - Vildagliptin in other countries.
  - Lack "high" GLP-1 effects.
- GLP-1 receptor agonists:
  - Subcutaneous injection.
  - Exenatide, liraglutide, weekly exenatide LAR.
  - Others in development.

DPP-4 Inhibitors

- Oral – sitagliptin, saxagliptin, linagliptin, alogliptin.
- Efficacy:
  - Moderate A1C improvement potency.
  - Higher potency when combined with metformin.
  - Weight neutral.
  - Improved CV risk profile.
- Safety:
  - No added hypoglycemia unless used with sulfonylurea.
  - No GI side effects.
  - Pancreatitis - not seen in large data base analyses.
- Dosing adjustments for renal dysfunction EXCEPT linagliptin.

Comparison of DPP-4 Inhibitors

<table>
<thead>
<tr>
<th>Dose</th>
<th>Sitagliptin</th>
<th>Saxagliptin</th>
<th>Linagliptin</th>
<th>Alogliptin</th>
</tr>
</thead>
<tbody>
<tr>
<td>25, 50, 100 mg once daily</td>
<td>2.5, 5.0 mg once daily</td>
<td>5 mg once daily</td>
<td>6.25, 12.5, 25 mg daily</td>
<td></td>
</tr>
<tr>
<td>T1/2</td>
<td>12.4 h</td>
<td>2.2 to 3.8 h</td>
<td>&gt; 113 h</td>
<td>21 h</td>
</tr>
<tr>
<td>Elimination</td>
<td>Kidney (mostly unchanged)</td>
<td>Liver and kidney active metabolites</td>
<td>Liver, &lt;5% renal</td>
<td>Kidney (mostly unchanged)</td>
</tr>
<tr>
<td>Dose adjustments for renal impairment</td>
<td>Yes</td>
<td>Yes</td>
<td>None</td>
<td>Yes</td>
</tr>
<tr>
<td>Drug interaction potential</td>
<td>Low</td>
<td>Strong CYP3A4 inhibitors</td>
<td>Strong CYP3A4 inhibitors</td>
<td>Low</td>
</tr>
</tbody>
</table>

GLP-1 Receptor Agonists

- Subcutaneous injectable – exenatide, liraglutide, weekly exenatide.
- Efficacy:
  - Greater reduction in A1c than DPP-4 inhibitors.
  - Potential for weight loss.
  - Improved CV risk profile.
- Safety:
  - Major side effect GI - nausea/vomiting, diarrhea.
  - No added hypoglycemia unless used with sulfonylurea.
  - C-cell hyperplasia and medullary cancer in rodents.
  - Pancreatitis - not seen in large data base analyses.

GLP-1 Receptor Agonists

Characteristics of Marketed GLP-1 RAs

<table>
<thead>
<tr>
<th>Exenatide BID</th>
<th>Liraglutide</th>
<th>Exenatide ER</th>
</tr>
</thead>
<tbody>
<tr>
<td>Protraction mechanism</td>
<td>GLP-1 analogue</td>
<td>GLP-1 analogue</td>
</tr>
<tr>
<td>Half-life/dosing</td>
<td>2.4 hours × 2 daily, before meals</td>
<td>13 hours</td>
</tr>
<tr>
<td>Microsphere delivery for exenatide ER</td>
<td>Glycylated polymer microspheres</td>
<td>Glycylated polymer microspheres</td>
</tr>
</tbody>
</table>

*Median half-life.

Meta-Analysis: Weight Loss with GLP-1 RAs

Exendin-4 extended release (ER) vs control:
-2.8 (95% CI: -3.9 to -1.8)
Liraglutide control:
-2.8 (95% CI: -3.9 to -1.8)
Exenatide BID control:
-2.8 (95% CI: -3.9 to -1.8)

Weight Change (kg)

- In head-to-head trials, weight loss was similar for LIRA and EXN ER.
- Head-to-head, weight loss was greater with LIRA (3.6 kg) vs EXN ER (2.7 kg, P = .001).
- Loss sustained for 2.2 years.
1. Control includes PBO, OADs, or insulin.

Effect of GLP-1 Receptor Agonists on CVD Risk Factors

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Exenatide 10 mcg twice daily (3.5 years)</th>
<th>Liraglutide 1.2 mg once daily (26 weeks)</th>
<th>Exenatide LAR 2.0 mg once weekly (1 year)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systolic BP (mm Hg)</td>
<td>-3.5*</td>
<td>-4.7*</td>
<td>-4.2*</td>
</tr>
<tr>
<td>Diastolic BP (mm Hg)</td>
<td>-3.3*</td>
<td>-2.2</td>
<td>-2.6*</td>
</tr>
<tr>
<td>Total cholesterol (mg/dL)</td>
<td>-10.8*</td>
<td>-8.1</td>
<td>7.3*</td>
</tr>
<tr>
<td>LDL cholesterol (mg/dL)</td>
<td>-10.9*</td>
<td>-2.2</td>
<td>-1.2</td>
</tr>
<tr>
<td>HDL cholesterol (mg/dL)</td>
<td>8.5</td>
<td>-2.8</td>
<td>-1.2</td>
</tr>
<tr>
<td>Triglycerides (mg/dL)</td>
<td>-44.4*</td>
<td>-40.0*</td>
<td>-40.6*</td>
</tr>
<tr>
<td>Free fatty acids (mmol/L)</td>
<td>NR</td>
<td>-1.2</td>
<td>NR</td>
</tr>
</tbody>
</table>

*P < 0.05 vs baseline; †P < 0.05 vs placebo.

Hypoglycemia With GLP-1 RAs: with and without Sulfonylureas in Head-to-Head Trials

- Only 2 cases of major hypoglycemia* (Exenatide BID = 8 in LEAD-1)1,2
- Less minor hypoglycemia with LIRA vs Exenatide BID (1.80 vs 2.80 events per P-Y; P = .013).1

Properties of GLP-1 Receptor Agonists

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Exenatide Twice Daily</th>
<th>Liraglutide Once Daily</th>
<th>Exenatide LAR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Description</td>
<td>Synthetic exenatide</td>
<td>Human GLP-1 analog</td>
<td>Exenatide extended release</td>
</tr>
<tr>
<td>Half-life</td>
<td>2.4 h</td>
<td>12-14 h</td>
<td>&gt; 1 wk</td>
</tr>
<tr>
<td>Postprandial glucose</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
</tr>
<tr>
<td>Postprandial plasma glucose</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
</tr>
<tr>
<td>A1C (%)</td>
<td>≈ 0.9</td>
<td>≈ 1.5-1.8</td>
<td>≈ 1.7</td>
</tr>
<tr>
<td>Weight change (kg)</td>
<td>Approximate decrease of 0.5 kg</td>
<td>Varies across class and with study duration</td>
<td></td>
</tr>
</tbody>
</table>

*Minor hypoglycemia = self-treatable, with plasma glucose < 55 mg/dL; major hypoglycemia = requiring third-party assistance.

Common adverse effects: Nausea
**Exenatide LAR vs Twice-Daily Exenatide 30 Weeks**

- EXN 10 mcg twice daily (n=147)
- EXN LAR 2.0 mg once weekly (n=148)

### A1C<7.0% (% patients)

- Baseline: 8.3%
- Week 26: 6.5%
- Week 30: 6.2%

### A1C change (%)

- Baseline: 0%
- Week 26: -1.5%
- Week 30: -1.9%

### Weight change (kg)

- Baseline: 0 kg
- Week 26: -25 kg
- Week 30: -26 kg

### FPG change (mg/dL)

- Baseline: 8.3 mg/dL
- Week 26: 6.1 mg/dL
- Week 30: 5.9 mg/dL

**Exenatide BID Reduces PPG More Than Exenatide QW and Liraglutide**

- EXN BID vs EXN QW and LIRA

### DURATION-1: Meal Tolerance Testing

- Significantly greater PPG decreases with EXN BID vs LIRA
  - Breakfast estimated treatment difference: 24 mg/dL
  - Dinner estimated treatment difference: 18 mg/dL

### LEAD-6: SMBG

- Nausea may resolve more quickly with some agents

**26-Week Comparison of Liraglutide and Exenatide Twice Daily**

- Baseline A1c: 8.2% (LIRA) vs 8.1% (EXN)
- Change in A1c: -0.8% (LIRA) vs -1.1% (EXN)
- Weight change: 2.9 kg (LIRA) vs 3.2 kg (EXN)

**Reports of Nausea Vary by Agent**

- The proportion of patients reporting nausea is lower with some agents

**Addition of Twice-daily Exenatide to Glargine Insulin-treated Type 2 Diabetes**

- N=259. Baseline A1c: 8.5% (placebo) and 8.3% (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

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### Hot Topics

**Addition of Twice-daily Exenatide to Glargine Insulin-treated Type 2 Diabetes**

- N=259. Baseline A1c: 8.5% (placebo) and 8.3% (exenatide)
- Better improvement A1c: -1.7% exenatide versus -1.0% placebo
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**Liraglutide Plus Insulin Detemir**

- Co-administration of liraglutide with insulin detemir demonstrates additive pharmacodynamic effects.
- Supplementation of metformin with liraglutide and then insulin detemir was well tolerated in the majority of patients, with good glycemic control, sustained weight loss, and very low hypoglycemia rates. Translated into clinical practice, and extrapolating from all patients who completed run-in, sequential intensification enabled approximately three-quarters of patients to achieve an A1C <7%.

*Sequential Intensification of Metformin Treatment in Type 2 Diabetes With Liraglutide Followed by Randomized Addition of Basal Insulin Prompted by A1C Targets*  
Liraglutide-Detemir Study Group Diabetes Care, 2012

**Incretin Plus Basal Insulin**

- Incretin plus basal insulin therapy has a logical rationale, providing efficacy and tolerability in the treatment of T2DM.
- Starting with an incretin-based agent and then adding insulin rather than vice versa avoids the complexity of having to down-titrate insulin, and any nausea issues with GLP-1 RA are likely to have subsided using this sequence.

**Incretin Plus Basal Insulin**

- While we advocate the introduction of incretin-based therapy prior to insulin, we also stress that patients suboptimally controlled on high-dose basal insulin can nevertheless benefit from the addition of an incretin.
- Given the evidence from combination studies, a DPP-IV inhibitor at mealtimes with basal/premixed insulin or a short-acting GLP-1 receptor agonist (b.i.d. or o.d.) with basal/premixed insulin might also be considered depending upon the individual patient’s needs and dietary habits.

**Take Home Pearls on Incretins for Clinical Practice**

**GLP-1 Agonists**
1. Increase glucose dependent insulin secretion
2. Decrease glucose dependent glucagon secretion
3. Slow gastric emptying
4. Increase satiety (decreasing appetite)
5. Promote weight reduction
6. Beneficial effects on cardiovascular risk factors
7. Decrease fasting and postprandial glucose with short acting agonists primarily affecting postprandial glucose
8. Low risk of hypoglycemia

**DDP-IV Inhibitors**
1. Increase glucose dependent insulin secretion
2. Decrease glucose dependent glucagon secretion
3. Well tolerated oral agents
4. Weight neutral
5. Low risk of hypoglycemia

**Case 1**

- 56-year-old African-American woman presents to your office for continued follow up for T2DM and hypertension.
- Currently taking: metformin 1000 mg BID, glimepiride 4 mg daily and losartan 100 mg daily.
- Patient has been adherent to medication therapy and has gained weight despite counseling and lifestyle changes.

| BMI: | 32 kg/m² |
| Waist: | 39 inches |
| BP: | 146/92 mm Hg (bilaterally) |
| Random glucose: | 207 mg/dL |
| A1C: | 8.2% |
| eGFR: | >60 mL/min/1.73 m² |
| Total cholesterol: | 224 mg/dL |
| HDL-C: | 41 mg/dL |
| TG: | 225 mg/dL |
| LDL-C: | 138 mg/dL |
Case 1

After discussing various treatment options, you initiate treatment with a GLP-1 agonist and a statin in addition to her existing therapy. Continuing with dietary counseling, exercise and advising her to self monitor blood glucose daily before breakfast and 2 hours after supper.

She returns in 12 weeks with the following data:

- A1C: 7.1%
- TG: 145 mg/dL
- Pre-prandial glucose: 108 to 114 mg/dL
- Total chol: 164 mg/dL
- Post-prandial glucose: 139 to 149 mg/dL
- HDL-C: 44 mg/dL
- LDL-C: 91 mg/dL
- Weight: down 5 lbs

Case 2: Steven

- Male
- Age: 72 years
- BMI: 28 kg/m²
- T2DM for 8 years
- Active, self-sufficient
- Medications
  - Metformin 2000 mg/d
  - Glimepiride 4 mg/d
- A1C: 8.9%
- Comorbidities/safety concerns
  - Congestive heart failure
  - Mild to moderate renal insufficiency (eGFR 50 mL/min/1.73 m²)

GLP-1 RA Safety

Javier Morales, MD
St. Francis hospital
Vice President
Principal Clinical Trials Investigator
Advanced Internal Medicine Group, PC
Great Neck, New York

GLP-1 RA Cardiovascular Safety: Post Hoc Analyses of Pooled Clinical Trial Data

<table>
<thead>
<tr>
<th>Study</th>
<th>Comparators</th>
<th>Outcome</th>
<th>Risk Assessment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ratner et al²</td>
<td>EXN BID (n = 2316) Non-EXN BID (n = 1629)³</td>
<td>CV death, stroke, MI; ACS; revascularization</td>
<td>RR (95% CI) 0.70 (0.38-1.31)</td>
</tr>
<tr>
<td>Marso et al⁴</td>
<td>LIRA (n = 4257) Non-LIRA (n = 2381)⁵</td>
<td>CV death, stroke, MI</td>
<td>RR (95% CI) 0.73 (0.38-1.41)</td>
</tr>
</tbody>
</table>

- Long-term trials to further evaluate the impact of GLP-1 RAs on the occurrence of CV events are in progress³
  - LIRA (LEADER—NCT01179048): results anticipated in 2016
  - EXN QW (EXSCEL—NCT01144338): results anticipated in 2017
  - LIXI (ELIXA—NCT01147250)⁶: results anticipated in 2014

ACS, acute coronary syndrome; CV, cardiovascular; EXN BID, exenatide twice daily; EXN QW, exenatide extended-release; IR, incidence ratio; LIRA, liraglutide; MI, myocardial infarction; RR, risk ratio.

² Insulin or placebo; b Active comparator or placebo; c In patients who have experienced acute coronary syndrome; d LIXI not FDA approved.

4. Long-term trials to further evaluate the impact of GLP-1 RAs on the occurrence of CV events are in progress³
5. LIRA (LEADER—NCT01179048): results anticipated in 2016
6. EXN QW (EXSCEL—NCT01144338): results anticipated in 2017
7. LIXI (ELIXA—NCT01147250): results anticipated in 2014

Outline

- Cardiovascular safety
- Specific precautions
  - Acute renal failure/renal insufficiency
  - Nausea
  - Medullary Thyroid Cancer
  - Pancreatitis and Pancreatic Cancer
- Use in patients with comorbid conditions (ie, some elderly patients)
- Injection techniques
Evidence Regarding Renal Impairment With GLP-1 RAs

- Evidence does not indicate direct renal toxicity with GLP-1 RAs 1-3
  - Renal impairment (RI) impacts clearance of EXN but not LIRA 1,4,5
  - Hypovolemia due to nausea/vomiting may worsen renal function 1
- Renal impairment has been reported in patients taking GLP-1 RAs 1
  - Reversed in many cases with supportive treatment and discontinuation of potentially causative agents
  - Sometimes required hemodialysis or transplantation
- Some cases occurred in patients who: 1,6-9
  - Experienced nausea, vomiting, diarrhea, dehydration
  - Took medications known to affect renal function or hydration status
  - Had no known underlying renal disease


Recommendations for GLP-1 RA Use: Possible Renal Impairment Risk

- Recommendations
  - Use with caution in patients with RI or renal transplantation, especially when initiating or escalating doses
  - Do not use EXN BID or EXN QW in patients with severe RI or ESRD

ESRD, end-stage renal disease; EXN BID, exenatide twice daily; ESRD, end-stage renal disease; EXN QW, exenatide extended-release; LIRA, liraglutide; RI, renal impairment.

Prescribing Information Precautions

<table>
<thead>
<tr>
<th>Prescribing Information</th>
<th>EXN BID</th>
<th>LIRA</th>
<th>EXN QW</th>
</tr>
</thead>
<tbody>
<tr>
<td>Renal impairment</td>
<td>Not in severe RI (CrCl &lt; 30 mL/min) or ESRD</td>
<td>Use with caution</td>
<td>Not in severe RI (CrCl &lt; 30 mL/min) or ESRD</td>
</tr>
</tbody>
</table>

Nausea: Exenatide QW Versus Exenatide BID and Exenatide QW Versus Liraglutide

- Significantly lower vs EXN BID


Using GLP-1 Receptor Agonists in Early-stage Diabetes and Special Circumstances

- DPP-4 inhibitors and GLP-1 receptor agonists
- Mechanisms of action
- GLP-1 receptor agonists
- Monotherapy
- Metformin background
- vs sitagliptin
- AACE recommendations for use in pre-diabetes (currently off-label)
- Current questions regarding GLP-1 RA and
  - Thyroid cancer
  - Pancreatitis, pancreatic cancer
  - Other histological changes (endocrine pancreas)
- Outlook
Liraglutide: Prevalence of Prediabetes at 1 and 2 years


**Evidence Regarding Thyroid Cancer Risk With GLP-1 RAs**

- Rodents, but not nonhuman primates, developed thyroid C-cell tumors when treated with GLP-1 RAs.
- Unknown whether GLP-1 RAs cause C-cell tumors in humans; relevance of animal studies cannot be determined through trials because MTCs are rare.
  - Clinical trials:
    - LIRA: 1.5 PTCa cases per 1000 P-Yrs vs 0.5 in controls, no confirmed MTCs
    - EXN BID: 0.3 thyroid neoplasms per 100 P-Yrs vs 0 in controls
  - Meta-analysis of published studies:
    - No reported thyroid malignancies with EXN
    - No increased thyroid cancer risk with LIRA (OR 1.54 [95% CI 0.40-6.02])

**Recommendations for GLP-1 RA Use: Possible Thyroid Tumor Risk**

<table>
<thead>
<tr>
<th>Prescribing Information Contraindications</th>
<th>EXN BID</th>
<th>LIRA</th>
<th>EXN QW</th>
</tr>
</thead>
<tbody>
<tr>
<td>Possible thyroid tumor risk: do not use if history of MTC or MEN2</td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
</tbody>
</table>

- **Recommendations**
  - LIRA and EXN QW are contraindicated in patients with MEN2 or a personal or family history of MTC.
  - Counsel patients regarding MTC risk and symptoms of thyroid tumors.
  - Value of routine calcitonin and/or ultrasound monitoring is uncertain; such monitoring may lead to unnecessary procedures.
  - Patients with thyroid nodules or elevated serum calcitonin levels identified for other reasons should be sent to an endocrinologist.
  - To monitor potential associations, report MTC to state cancer registry, regardless of treatment:

**Black Box Safety Consideration**

- Liraglutide and exenatide ER are contraindicated in patients with multiple endocrine neoplasia syndrome type 2 (MEN 2) or a personal or family history of medullary thyroid cancer (MTC), a relatively rare form of cancer.
- Differentiate for patients that these are rare types of cancers and not the same as thyroid cancers that are more common in the general population.

**Patient Counseling: Thyroid**

- Call health care professional if lump or swelling in your neck, hoarseness, trouble swallowing, or shortness of breath.
  - These may be symptoms of thyroid cancer.
- Human risk? To date, no human cases reported, but precancerous cells have been reported.
- ¼ of MTC in humans has GLP-1 binding receptors.
GLP-1 RA Safety

Outline
• Cardiovascular safety
• Specific precautions
  – Acute renal failure/renal insufficiency
  – Nausea
  – Medullary Thyroid Cancer
  – Pancreatitis and Pancreatic Cancer
• Use in patients with comorbid conditions (ie, some elderly patients)
• Injection techniques

Characteristics of Patients with T2DM at Risk for Pancreatitis

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Pancreatitis (Cases)</th>
<th>No Pancreatitis (Controls)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>[% with risk factor present]</td>
<td></td>
</tr>
<tr>
<td>Hypertriglyceridemia</td>
<td>13</td>
<td>8</td>
</tr>
<tr>
<td>Alcohol use</td>
<td>3</td>
<td>&lt; 1</td>
</tr>
<tr>
<td>Gallstones</td>
<td>9</td>
<td>1</td>
</tr>
<tr>
<td>Tobacco abuse</td>
<td>16</td>
<td>6</td>
</tr>
<tr>
<td>Obesity</td>
<td>20</td>
<td>10</td>
</tr>
<tr>
<td>Biliary/pancreatic cancer</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>Cystic fibrosis</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Neoplasm</td>
<td>30</td>
<td>18</td>
</tr>
</tbody>
</table>

Recommendations for GLP-1 RA Use: Possible Pancreatitis Risk

Prescribing Information

<table>
<thead>
<tr>
<th>Precautions</th>
<th>EXN BID</th>
<th>LIRA</th>
<th>EXN QW</th>
</tr>
</thead>
<tbody>
<tr>
<td>History of pancreatitis</td>
<td>Consider other agents</td>
<td>Use with caution</td>
<td>Consider other agents</td>
</tr>
</tbody>
</table>

• Recommendations
  – Educate patients and monitor for signs and symptoms
  – Ask about medical history of pancreatitis
  – Discontinue promptly if pancreatitis symptoms occur (eg, persistent severe abdominal pain that may or may not be accompanied by vomiting)
  – If acute pancreatitis is confirmed, do not restart GLP-1 RA
  – Report cases of pancreatitis to www.fda.gov/medwatch

Evidence Regarding Acute Pancreatitis Risk With GLP-1 RAs

• Cases have been reported in patients taking GLP-1 RAs
• Pancreatitis risk is 1.5- to 3-fold higher in individuals with diabetes
• Several analyses of clinical trial and insurance claims data demonstrated no increased risk with exenatide or liraglutide
• Recent independent analyses of large insurance databases yielded mixed results
• Cases have been reported in patients taking DPP-4 inhibitors

Pancreatic Neuroendocrine Tumors (Microadenomas) After Incretin-based Diabetes Therapy

Pancreatic glucagon expressing neuroendocrine tumor and microadenoma. (A) Grossly visible lesion and (B) corresponding H&E-stained section of the clinically undetected glucagon expressing neuroendocrine tumor in the pancreas of nPOD case 6206, type 2 diabetes after prior sitagliptin therapy. (C) Gross specimen and (D) corresponding H&E-stained section of a glucagon expressing microadenoma in case nPOD case 6206, type 2 diabetes after prior sitagliptin therapy. Inset shows high-power view of representative cells stained for glucagon by immunohistochemistry.
GLP-1 RA Safety

Outline
  • Cardiovascular safety
  • Specific precautions
    – Acute renal failure/renal insufficiency
    – Nausea/GI intolerance
    – Medullary Thyroid Cancer
    – Pancreatitis and Pancreatic Cancer
  • Use in patients with comorbid conditions (e.g., elderly patients; concomitant medications)

Framework for Considering Glycemic Goals in Older Adults With Diabetes

<table>
<thead>
<tr>
<th>Patient Characteristics/Health Status</th>
<th>Rationale</th>
<th>Reasonable A1C Goal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Healthy—free coexisting chronic illnesses, intact cognitive and functional status</td>
<td>Longer remaining life expectancy</td>
<td>&lt; 7.5%</td>
</tr>
<tr>
<td>Complex/intermediate—multiple coexisting illnesses or 2+ functional/ADL impairments or mild to moderate cognitive impairment</td>
<td>Intermediate remaining life expectancy; high treatment burden; hypoglycemia vulnerability, fall risk</td>
<td>&lt; 8.0%</td>
</tr>
<tr>
<td>Very complex/poor health—long-term care or end-stage chronic illnesses or moderate to severe cognitive impairment or 2+ ADL dependencies</td>
<td>Limited remaining life expectancy makes benefit uncertain</td>
<td>&lt; 8.5%*</td>
</tr>
</tbody>
</table>

ADL, activities of daily living
* Lower goal may be set if achievable without recurrent or severe hypoglycemia or undue treatment burden

GLP-1 RAs in Patients With Comorbidities: Older Patients

“Classic” Diabetes Comorbidities

- Renal disease:
  - 3X higher ESRD prevalence in patients > 65 y with diabetes vs those without
- CVD:
  - 43% of patients 65-74 y and 55% of patients > 75 y have CVOD
- 2X higher CHF prevalence in patients > 65 y with diabetes vs those without
- Hepatic disease:
  - Nearly 75% of patients ≥ 60 y have NAFLD

Geriatric Syndromes

- Cognitive dysfunction
- Functional impairment
- Falls and fractures
- Polypharmacy
- Depression
- Vision and hearing impairment
- Pain from neuropathy or other causes
- Urinary incontinence

GLP-1 RA Effects in Older and Younger Patients: Pooled Analyses of Phase 3 Trials

<table>
<thead>
<tr>
<th>Clinical Outcome</th>
<th>EXN BID (10 mcg) 16 trials</th>
<th>EXN QW (2.0 mg) 7 trials</th>
<th>LIRA (1.8 mg) 6 trials</th>
<th>LIXI (20 mcg) 6 trials</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 65 y</td>
<td>≥ 65 y</td>
<td>≥ 65 y</td>
<td>≥ 65 y</td>
<td>≥ 65 y</td>
</tr>
<tr>
<td>&lt; 65 y</td>
<td>≥ 65 y</td>
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<td>≥ 65 y</td>
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</tbody>
</table>

Hypoglycemia, major and minor, %

- EXN BID: 10% vs 10%
- EXN QW: 8% vs 8%
- LIRA: 14% vs 15%
- LIXI: 2.4% vs 0.5%

Nausea, %

- EXN BID: 38 vs 41%
- EXN QW: 15 vs 11%
- LIRA: 11 vs 12%
- LIXI: 7 vs 7%

Vomiting, %

- EXN BID: 14 vs 14%
- EXN QW: 9 vs 7%
- LIRA: 14 vs 14%
- LIXI: 13 vs 13%

Diarrhea, %

- EXN BID: 11 vs 11%
- EXN QW: 10 vs 11%
- LIRA: 12 vs 11%
- LIXI: 8 vs 8%

Hypoglycemia With GLP-1 RAs: With and Without Sulfonylureas in Head-to-Head Trials

<table>
<thead>
<tr>
<th>Clinical Outcome</th>
<th>LIRA (1.8 mg QD)</th>
<th>EXN BID (10 mcg QD)</th>
<th>EXN QW (2.0 mg QW)</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥ 65 y</td>
<td>10 vs 10 vs 10</td>
<td>10 vs 10 vs 10</td>
<td>10 vs 10 vs 10</td>
</tr>
<tr>
<td>&lt; 65 y</td>
<td>10 vs 10 vs 10</td>
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Hypoglycemia With GLP-1 RAs: With and Without Sulfonylureas in Head-to-Head Trials

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<tr>
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<th>LIRA (1.8 mg QD)</th>
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<tr>
<td>≥ 65 y</td>
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<tr>
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<td>10 vs 10 vs 10</td>
<td>10 vs 10 vs 10</td>
<td>10 vs 10 vs 10</td>
</tr>
</tbody>
</table>

Hypoglycemia With GLP-1 RAs: With and Without Sulfonylureas in Head-to-Head Trials

- Only 2 cases of major hypoglycemia (EXN BID vs SU in LEAD-4/Y3)
- Less minor hypoglycemia with LIRA vs EXN BID (1.5 vs 2.0 episodes/patient)
- No increased risk with LIRA vs EXN BID (1.5 vs 2.0 episodes/patient)
GLP-1 RA Safety

Outline

- Cardiovascular safety
- Specific precautions
  - Acute renal failure/renal insufficiency
  - Nausea
  - Medullary Thyroid Cancer
  - Pancreatitis and Pancreatic Cancer
- Use in patients with comorbid conditions (ie, some elderly patients)
- Injection techniques

GLP-1 RAs Are Administered by Subcutaneous Injection

<table>
<thead>
<tr>
<th>GLP-1 RA</th>
<th>Administration</th>
<th>Dose Options</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exenatide (Pen)</td>
<td>BID</td>
<td>5 mcg—orange, 10 mcg—yellow</td>
</tr>
<tr>
<td>Liraglutide (Pen)</td>
<td></td>
<td>Adjust to deliver dose (0.6 mg, 1.2 mg, or 1.8 mg)</td>
</tr>
<tr>
<td>Exenatide QW</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Exenatide BID (Pen)
- Start with 5 mcg, increase to 10 mcg after 1 month
- Inject within 60 min of 2 main meals

Liraglutide (Pen)
- Adjust to deliver dose (0.6 mg, 1.2 mg, or 1.8 mg)
- Start with 0.6 mg, increase after 1 week to 1.2 mg
- May increase to 1.8 mg, if needed
- Inject once daily, any time

Exenatide QW
- Inject immediately after suspension
- Prior exenatide BID treatment not required
- Inject missed dose only if next dose is ≥3 days away
- Inject single 2-mg dose once weekly, any time

US FDA. Drugs@FDA. http://www.accessdata.fda.gov/Scripts/cder/DrugsatFDA.

Smaller Pen Needle Size Is Effective and Preferred

- 4 mm × 32 G vs 5 mm × 31 G or 8 mm × 31 G
- 164 study participants
- Mean BMI: 31.0 kg/m²
- BMI range: 20 to 49 kg/m²
- 52% with BMI > 30 kg/m²
- No difference in glycemic control or safety among needle sizes
- Significantly lower pain scores for 4 mm vs 5 mm and 8 mm needles
- Equivalent glycemic control for obese vs nonobese participants

Preference (%) of participants

- 4 mm vs 8 mm
- 4 mm vs 5 mm

Preference

- Other—little more
- Other—lot more
- N/A
- Preference
- D4 mm—little more
- D4 mm—lot more


Smoothing the Transition to Injections

- Identify regimen with flexibility the patient needs/desires
  - EXN BID administer before 2 (largest) meals of day
  - LIRA, EXN QW—less frequent dosing
- Injection is relatively painless
  - Small, fine needle
  - Fatty tissue vs muscle
- “See one, do one, teach one.”
  - Have patient see/use pen and needle before leaving office
  - Refer patient to product-specific resources for starting treatment

1. US FDA. Drugs@FDA. http://www.accessdata.fda.gov/Scripts/cder/DrugsatFDA.

Summary: Label Recommendations for GLP-1 RA Use in Patients With T2DM

<table>
<thead>
<tr>
<th>GLP-1 RA</th>
<th>Indications and usage</th>
<th>Warnings, precautions, contraindications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exenatide BID</td>
<td>Adjunct to diet and exercise</td>
<td>Not first-line therapy</td>
</tr>
<tr>
<td>Liraglutide</td>
<td></td>
<td>Not use if history of MTC or MEN2</td>
</tr>
<tr>
<td>Exenatide QW</td>
<td></td>
<td>Do not use if history of MTC or MEN2</td>
</tr>
</tbody>
</table>

History of pancreatitis

- Consider other agents
- Use with caution
- Consider other agents

Renal impairment

- Not in severe RI or ESRD
- Use with caution
- Not in severe RI or ESRD

Increased risk of hypoglycemia with secretagogues/insulin

- X
- X
- X

Hypersensitivity

- X
- X
- X

MEN2, multiple endocrine neoplasia syndrome type 2; MTC, medullary thyroid carcinoma

Take Home Points

1. Individualize treatments according to patient needs
2. Know the guidelines
3. Counsel patients regarding risks and benefits of various therapies
4. Treating patients with diabetes not only means achieving glycemic, lipid and blood pressure goals, but reducing cardiovascular risk, progression of disease and beta cell deterioration
5. Choose those medications that will achieve these goals, provide your patients with the best quality of life and increase their compliance to therapy