Who Wants to be a Diabetologist?
Individualizing Type 2 Diabetes Therapy with GLP-1R Agonists
November 2013
(Part 1 of 2)

Pre-Test
This is a non-CME pre-test of the concepts discussed in this newsletter. At the end of the newsletter, click on the link provided to obtain free CME credit.

TOPIC: Individualizing Type 2 Diabetes Therapy with GLP-1R Agonists

Question 1 of 4

Which 1 of the following statements is true about glucagon-like peptide-1 receptor agonists?

A. Exenatide extended-release is given 2 times a week

B. Exenatide extended-release and liraglutide can be given without regard to meals

C. Exenatide twice-daily and liraglutide should be uptitrated over 1 week

D. Exenatide twice-daily should be administered within 1 hour before or 1 hour after a meal

Glucagon-like peptide-1 receptor agonists in chronic kidney disease and when hypoglycemia is a special concern

Since approval of the first glucagon-like peptide-1 receptor (GLP-1R) agonist in the United States in 2005, this group of medications has taken an increasingly prominent role in the recommended management of individuals with type 2 diabetes mellitus (T2DM). In this e-newsletter, the use of GLP-1R agonists in patients with kidney dysfunction, as well as their use when hypoglycemia is a special concern, will be explored. In an e-newsletter next month, the combined use of a GLP-1R agonist and basal insulin will be discussed.

The actions of the GLP-1R agonist on the incretin system produce several effects that are important in the treatment of patients with T2DM. First, the GLP-1R agonists stimulate insulin secretion and inhibit glucagon secretion, both in a glucose-dependent manner. In addition, the GLP-1R agonists slow the gastric emptying rate. The results of randomized clinical
Novo Nordisk, Inc. It has been edited and peer reviewed by The Journal of Family Practice.

Learning Objectives

• Provide an overview of the rationale and role of incretin-based therapy as described in updated practice guidelines for the management of persons with T2DM

• Compare the efficacy, safety, and tolerability of the incretin-based therapies currently available

• Describe strategies to individualize treatment with a GLP-1R agonist

Target Audience

Family physicians and clinicians with an interest in diabetes treatment and management

Sponsor Disclosure Statement

Edward Shahady, MD, discloses that he is on the advisory boards for Eli Lilly and Company, Janssen Pharmaceuticals, Inc., Novo Nordisk, Inc., and sanofi-aventis U.S. LLC and is on the speakers’ bureau for Merck & Co., Inc.

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trials with GLP-1R agonists as monotherapy or in combination with 1 or more glucose-lowering agents show a reduction in glycated hemoglobin (HbA\textsubscript{1c}) of 0.5% to 1.1% with exenatide twice daily (BID), 1.5% to 2.0% with exenatide once weekly (QW), and 0.5% to 1.5% with liraglutide.\textsuperscript{6,15-21} The GLP-1R agonists typically lower systolic blood pressure (BP) 1 to 7 mm Hg, but have little effect on diastolic BP.\textsuperscript{6,16,19,22-24} Of their effects on the lipid profile, the largest is on triglycerides, with a reduction of 12 to 40 mg/dL with the GLP-1R agonists.\textsuperscript{6,19,22,25,26} The GLP-1R agonists have been compared in head-to-head clinical trials and the differences are summarized in the Table.\textsuperscript{6,18,27,28}

<table>
<thead>
<tr>
<th>Table. Head-to-head comparison of glucagon-like peptide-1 receptor agonists\textsuperscript{6,18,27,28}</th>
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<tbody>
<tr>
<td><strong>HbA\textsubscript{1c} reduction</strong></td>
</tr>
<tr>
<td>Liraglutide 1.8 mg QD &gt; exenatide 10 mcg BID</td>
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<tr>
<td>Exenatide 2 mg QW &gt; exenatide 10 mcg BID</td>
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<td><strong>FPG reduction</strong></td>
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<td>Liraglutide 1.8 mg QD &gt; exenatide 10 mcg BID</td>
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<tr>
<td><strong>PPG reduction</strong></td>
</tr>
<tr>
<td>Exenatide 10 mcg BID = exenatide 2 mg QW</td>
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<tr>
<td>Exenatide 10 mcg BID ≥ liraglutide 1.8 mg QD</td>
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<tr>
<td><strong>Nausea</strong></td>
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<tr>
<td>Exenatide 10 mcg BID &gt; liraglutide 1.8 mg QD</td>
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<tr>
<td>Exenatide 10 mcg BID &gt; exenatide 2 mg QW</td>
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<tr>
<td><strong>Proportion of patients who achieved HbA\textsubscript{1c} &lt;7%</strong></td>
</tr>
<tr>
<td>Liraglutide 1.8 mg QD &gt; exenatide 10 mcg BID</td>
</tr>
<tr>
<td>Exenatide 2 mg QW &gt; exenatide 10 mcg BID</td>
</tr>
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</table>

Abbreviations: BID, twice daily; FPG, fasting plasma glucose; HbA\textsubscript{1c}, glycated hemoglobin; PPG, postprandial glucose; QD, once daily; QW, once weekly.

CASE STUDY

A 67-year-old white male was diagnosed with T2DM 8 years ago. In the past 3 months, he has experienced 4 episodes of confirmed hypoglycemia (blood glucose <70 mg/dL).

• Past medical history: essential hypertension for 15 years; nonproliferative retinopathy; sleep apnea
• Social history: lives alone; smoker; 1 glass of wine before dinner
• Physical examination: BP, 142/90 mm Hg; weight, 194 lb; body mass index (BMI), 30 kg/m\textsuperscript{2}; 1+ distal sensory neuropathy; diabetic retinopathy
• Current treatment
  • Metformin 850 mg BID, glyburide 10 mg once daily, enalapril 20 mg once daily
  • Simvastatin 40 mg once daily
  • Stopped taking aspirin and lovastatin a year ago
  • Exercise: previously walked for 30 minutes daily; now exercises less due to fatigue and balance issues
• Laboratory
  • Total cholesterol, 245 mg/dL; low-density lipoprotein cholesterol (LDL-C), 135 mg/dL; high-density lipoprotein cholesterol (HDL-C), 38 mg/dL; triglycerides, 350 mg/dL; non–HDL-C, 207 mg/dL
  • Serum creatinine, 1.9 mg/dL; estimated glomerular filtration rate (eGFR), 36 mL/min/1.73 m\textsuperscript{2}; spot urine microalbumin ratio, 75 mcg/mg
  • HbA\textsubscript{1c} levels since diagnosis: see table below
Jeffrey R. Unger, MD, discloses that he is on the advisory boards for Abbott Laboratories, Genentech, Inc., Halozyme, Inc., Hoffmann-La Roche, Inc., and sanofi-aventis U.S. LLC. He discloses that he is on the speakers’ bureaus for Janssen Pharmaceuticals, Inc., and Valeritas, Inc., and receives a royalty from Lippincott (Publishing).
Appropriateness of other therapy

Patients with diabetes require comprehensive care to reduce their risk of cardiovascular and other complications of diabetes. One important change to his treatment plan is to reinitiate low-dose aspirin unless the patient had a compelling reason to discontinue it previously. To achieve the BP goal of <130/80 mm Hg, intensification of his antihypertensive therapy is needed. One option is to increase the dose of enalapril as tolerated. Alternatively, an angiotensin receptor blocker, such as losartan 50 mg once daily, could be initiated and enalapril discontinued. In addition, consideration could be given to starting a low-dose diuretic such as hydrochlorothiazide 12.5 mg once daily.

Since his eGFR has declined and is approaching 30 mL/min/1.73 m², the level below which simvastatin and most statins should be used cautiously, consideration should be given to discontinuing simvastatin and starting atorvastatin. Atorvastatin can be used safely in individuals with severe renal dysfunction. Although the patient’s triglyceride level is elevated, it is <500 mg/dL. Therefore, the immediate focus should be on achieving the LDL-C goal of <70 mg/dL, as this poses a greater cardiovascular risk than his mild hypertriglyceridemia. Once the LDL-C is <70 mg/dL, the hypertriglyceridemia can be addressed if the triglyceride level remains above 200 mg/dL and his non–HDL-C level is above 100 mg/dL.

In summary, the following is the treatment plan for this patient:

- Discontinue glyburide, simvastatin
- Continue metformin
- Increase enalapril to 25 mg once daily
- Begin
  - Liraglutide 0.6 mg once daily; increase to 1.2 mg once daily after 1 week or as tolerated
  - Educate about adverse events such as nausea, vomiting, dehydration
    - Hydrochlorothiazide 12.5 mg once daily
    - Atorvastatin 20 mg once daily at bedtime
    - Aspirin 81 mg once daily
- Avoid use of nonsteroidal anti-inflammatory drugs
- Monitor fasting blood glucose daily until target achieved, then first 7 days of each month
- Repeat tests for HbA₁c and eGFR in 2 to 3 months
- Monitor for chronic kidney disease-induced anemia and mineral abnormalities
- Refer to 1-800-QUIT-NOW for help with smoking cessation
- Consider consultation with a nephrologist

For free CME credit related to the content of this newsletter, please visit http://www.iafp.com/education and click on "Nov 2013 Who Wants to be a Diabetologist?".

References
8. Chatterjee DJ, Khotapishetty S, Hladic M, Spencer GR, Litwin JS. Absence of QTc...


