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

FREE 1.0 CME CREDIT

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

Question 1 of 4

Which 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

Am I correct? >>

Use of a glucagon-like peptide-1 receptor agonist in combination with basal insulin
The 3 glucagon-like peptide-1 receptor (GLP-1R) agonists currently approved in the United States—exenatide for twice-daily administration, exenatide extended-release for once-weekly administration, and liraglutide for once-daily administration—are all indicated as an adjunct to diet and exercise to achieve glycemic control in persons with type 2 diabetes mellitus (T2DM), a use that is well established.[13-18] The efficacy and safety of the GLP-1R agonists as a component of dual and triple glucose-lowering therapy have also been shown.[19-27] Recently, evidence concerning the use of a GLP-1R agonist in combination with basal insulin has emerged, a use that is now reflected in the 2013 algorithm and consensus statement issued by the American Association of Clinical Endocrinologists.[4] The combined use of a GLP-1R agonist and basal insulin is the focus of this e-newsletter. **[Note: exenatide extended-release for once-weekly administration is not approved for use in combination with insulin.]**

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

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CASE STUDY

Debbie is a 53-year-old white female diagnosed with T2DM 7 years ago. She has experienced a weight gain of 8 pounds over the past few months and has felt increasingly tired 1 to 2 hours after breakfast.

- Past medical history: otherwise healthy; her gynecologist indicated that she had "slightly elevated cholesterol" about a year ago
- Social history: executive director of a local nonprofit organization; lives with husband; no tobacco use; occasional alcohol use
- Physical examination: blood pressure (BP), 135/85 mm Hg; pulse, 78 beats/min; respiratory rate, 17 breaths/min; weight, 224 lb; body mass index (BMI), 38.4 kg/m^2
- Current treatment
  - Glimepiride 4 mg twice daily; basal insulin 48 U at bedtime
    - Initially treated with metformin, but stopped due to intolerable diarrhea
  - Poorly adherent with good nutrition; several business-related meals each week
    - Wants to start an exercise plan, but has not had the time to begin
- Laboratory
  - Glycated hemoglobin (HbA_{1c}) last week: 7.6%
  - Self-monitoring of blood glucose (SMBG) over past 5 weeks shows:
    - Prebreakfast blood glucose: 72-91 mg/dL
    - Random postprandial blood glucose: 219-242 mg/dL

Appropriateness of current glucose-lowering therapy

Debbie's blood glucose levels over the past 5 weeks indicate that her fasting glucose is well controlled, but her postprandial glucose remains high. The persistent postprandial hyperglycemia is likely responsible for her HbA_{1c} remaining above 7%, since the mean blood glucose level is increasingly determined by the postprandial glucose level as HbA_{1c} falls below 8% and approaches normal.[28] Adjustment of her therapy is needed to correct her postprandial hyperglycemia. To determine how her treatment plan should be modified, it is important to identify when she experiences postprandial hyperglycemia and the effect of the basal insulin on her blood glucose. To do this, further SMBG is needed.

- If the bedtime blood glucose is 50 mg/dL greater than the prebreakfast blood glucose, the basal dose is too high and the blood glucose is dropping in the night.
- If the prebreakfast blood glucose is 80 to 100 mg/dL and the bedtime glucose is not more than 50 mg/dL above the prebreakfast glucose, the basal dose is correct.
- If the prelunch blood glucose is higher than 180 mg/dL, the basal dose is unable to cover breakfast. In this case, a rapid-acting insulin analog is needed with breakfast to control the postbreakfast glucose.
- If the bedtime blood glucose is higher than 180 mg/dL, the basal dose is unable to cover dinner. In this case, a rapid-acting insulin analog is needed with dinner.

While modifying basal insulin therapy or adding prandial insulin are options, depending on the results of further SMBG, another approach would be to add a non-insulin agent that preferentially targets postprandial blood glucose. Options include an alpha-glucosidase inhibitor, colesevelam, a dipeptidyl peptidase-4 (DPP-4) inhibitor, a GLP-1R agonist, a meglitinide, pramlintide, a sodium glucose cotransporter-2 (SGLT-2) inhibitor, or a sulfonylurea.[4,5] The efficacy in lowering HbA_{1c} is modest with an alpha-glucosidase inhibitor or colesevelam, although achieving HbA_{1c} <7.0% is possible. Since colesevelam is associated with raising the triglyceride level, the type and magnitude of dyslipidemia should be assessed prior to initiation. Pramlintide would only be appropriate if therapy was initiated with prandial insulin. As she is already on a sulfonylurea, a meglitinide would not be appropriate. Consideration might even be given to discontinuing the sulfonylurea due to progressive beta-cell dysfunction and relatively poor glycemic durability with sulfonylureas.[29,30] Discontinuing or reducing the dose of the sulfonylurea can also be considered if treatment with a DPP-4 inhibitor, GLP-1R agonist, or SGLT-2 inhibitor is initiated, since the risk of hypoglycemia is increased with the combination compared to monotherapy with a DPP-4 inhibitor, GLP-1R agonist, or SGLT-2 inhibitor.[21,31-36]

Combined use of a GLP-1R agonist with basal insulin

The combination of a GLP-1R agonist and basal insulin has been investigated in several

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prospective clinical trials and retrospective analyses.[8-12,37-46] The results of the prospective trials show significantly greater reductions in HbA_{1c} levels and more patients achieving target HbA_{1c} with the combination compared with either a GLP-1R agonist or basal insulin alone.[8-12] For example, a 1-year study investigated the addition of liraglutide 1.8 mg once daily in patients inadequately controlled with metformin ± a sulfonylurea.[11] After 12 weeks, the mean HbA_{1c} level decreased from a baseline of 8.3% to 7.6%. Those who did not achieve HbA_{1c} <7.0% were randomized to 52 weeks open-label add-on treatment with insulin detemir or continuation without detemir. The addition of insulin detemir was associated with a decrease in HbA_{1c} of 0.50% compared with no change in those who continued liraglutide without the addition of insulin detemir (+0.01%) (P < .0001). More patients treated with insulin detemir achieved HbA_{1c} <7% at 52 weeks than those who continued liraglutide without insulin detemir (52% vs 22%, respectively; P < .0001).

In these prospective trials, the combination of exenatide twice-daily and insulin glargine was not associated with major hypoglycemia (patient unable to self-treat), while major hypoglycemia was experienced by <1% of those treated with insulin glargine alone.[8,9] Major hypoglycemia was not reported by patients treated with liraglutide as add-on therapy to insulin detemir, whereas 2 episodes of major hypoglycemia occurred in those whose insulin dose was increased to achieve glycemic control instead of adding liraglutide.[12] Minor hypoglycemia (patient able to self-treat) was generally more common with the combination of a GLP-1R agonist or basal insulin compared with either alone.[8,10,11] In contrast, a fourth trial found that minor hypoglycemia occurred more frequently in those whose insulin dose was increased to achieve glycemic control compared with those treated with the addition of liraglutide to insulin (31.0% vs 11.9%, respectively; P = .033).[12]

With respect to weight change, those treated with the combination of a GLP-1R agonist and basal insulin lost weight (–0.16 kg to –1.78 kg), while those treated with basal insulin alone gained weight (0.4 kg to 0.96 kg).[8-10] By comparison, the addition of insulin detemir attenuated the weight loss observed with the addition of liraglutide to metformin ± a sulfonylurea over 52 weeks (–0.1 kg vs –1.0 kg, respectively; P = .04).

A final benefit observed with the addition of a GLP-1R agonist to basal insulin has been a reduction in the total daily insulin dose, although this may be limited to patients with BMI ≥30 kg/m^2.[11,12] In a 12-week trial, the addition of liraglutide to basal insulin was associated with a 66% reduction in the total daily insulin dose (41.2 to 14.0 U/day), while a 28% increase in the total daily insulin dose (41.6 to 53.5 U/day) was observed in those whose insulin dose was adjusted to achieve glycemic control.[12] In other prospective trials, the dose of insulin was not decreased with the addition of a GLP-1R agonist, probably as a result of study design.[8,9]

Appropriateness of other therapy

Since patients with T2DM are at increased risk of cardiovascular and other complications, routine assessments of BP, blood lipids, kidney function, eyes, and skin are essential, as described by the American Diabetes Association.[47] The comment by Debbie's gynecologist about her "slightly elevated cholesterol" makes it clear that further investigation should be initiated without delay. Debbie's obesity and nutrition and exercise habits also need to be addressed as they serve as a basis of her T2DM and make glycemic control difficult.

At a 1-month follow-up, the primary care physician reviews Debbie's additional SMBG. Her results show frequent postprandial hyperglycemia following breakfast and lunch, indicating that the basal insulin is unable to cover breakfast and lunch. Debbie is unwilling to start prandial insulin because of the need to administer a dose after lunch. Debbie and her physician discuss the other options and conclude that initiating a GLP-1R agonist may be the best option, primarily because of its low risk of hypoglycemia (if the glimepiride is discontinued) and the fact that weight loss is experienced by most patients. Of the GLP-1R agonists, exenatide twice-daily is not a good choice for Debbie because she usually eats breakfast at work and she does not want to administer any medication at work. Since exenatide extended-release is not approved for use in combination with insulin, Debbie indicates a willingness to initiate liraglutide.

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Debbie and her primary care physician agree to the following treatment plan:

- Discontinue glimepiride
- Continue basal insulin
- Begin
  - Liraglutide once daily
    - Debbie is educated about adverse events such as nausea, vomiting, dehydration
  - Enalapril 5 mg once daily
  - Aspirin 81 mg once daily
- Reevaluate the need for lipid-lowering therapy based upon results of lipid profile (pending)
- Continue SMBG
- Repeat HbA_{1c} testing in 2 to 3 months
- Refer to a dietitian or certified diabetes educator for lifestyle management
- Schedule patient for a complete physical examination in 2 to 3 months

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