Combination Therapy with Insulins and GLP-1 Receptor Agonists

EDUCATIONAL OBJECTIVES

Upon completion of this activity, participants will be better able to:

1. Apply the American Diabetes Association and American Association of Clinical Endocrinologists guidelines in the management of patients with type 2 diabetes, with a specific focus on basal insulin therapy and glucagon-like peptide-1 (GLP-1) receptor agonists;
2. Compare and contrast the clinical profiles of the different basal insulins and GLP-1 receptor agonists and understand the unique pharmacokinetic and pharmacodynamic profile of each product;
3. Evaluate current data related to fixed-ratio combinations of GLP-1 receptor agonists and basal insulin, as well as products in development or under review;
4. Describe the clinical rationale and expected benefits of using combination therapy with complementary mechanisms of action; and
5. Formulate evidence-based treatment regimens that optimize control of both fasting and postprandial glucose levels.

Post-Test/Rationale

1. All of the following are characteristics of the pathophysiology of type 2 diabetes EXCEPT:
   
   A. Insulin resistance in peripheral tissues  
   B. Beta-cell dysfunction  
   C. Autoimmune destruction of beta-cells***  
   D. Increased glucagon release

Correct Answer: C

The pathophysiology of type 2 diabetes does not include autoimmune destruction; this describes type 1 diabetes mellitus.

2. According to the American Association of Clinical Endocrinologist guidelines, if hemoglobin A1c levels remain above goal after 3 months of treatment with metformin, the BEST agent to add next is:

   A. Liraglutide, a glucagon-like peptide-1 receptor agonist***  
   B. Pioglitazone, a thiazolidinedione  
   C. Glargine, a long-acting basal insulin  
   D. Glipizide, a sulfonylurea

Correct Answer: A

According to the American Association of Clinical Endocrinologist (AACE) guidelines, a glucagon-like peptide-1 (GLP-1) receptor agonist should be added next in this scenario. The
agents listed in the AACE guidelines are provided in order of preference and, therefore, although the other agents can be considered, they are not preferred over a GLP-1 receptor agonist.

3. All of the following agents significantly affect postprandial glucose excursions EXCEPT:

   A. Insulin lispro
   B. Liraglutide
   C. Metformin
   D. Repaglinide

   **Correct Answer: C**

   Metformin primarily affects fasting blood sugar; all other agents treat postprandial glucose excursions, which is evident by their mechanisms of action and timings of administration.

4. Which of the following is NOT true regarding glucagon-like peptide-1 receptor agonists?

   A. They can cause significant nausea in up to 40% of patients
   B. All of the agents must be administered 60 minutes prior to a meal for optimum effect
   C. They work, in part, by increasing satiety, decreasing gastric emptying, and decreasing food intake
   D. They are injected subcutaneously into the abdomen, thigh, or upper arm

   **Correct Answer: B**

   Most glucagon-like peptide-1 (GLP-1) receptor agonists can be administered without regard to meals. Twice-daily exenatide is the only exception and it should be administered 1 hour prior to the morning and evening meals. All of the other statements listed are true of GLP-1 receptor agonists.

5. Which pair correctly matches the glucagon-like peptide-1 receptor agonist to its recommended dosing schedule?

   A. Liraglutide: once weekly
   B. Albiglutide: once daily
   C. Exenatide: once weekly or twice daily, depending on the formulation
   D. Dulaglutide: twice weekly

   **Correct Answer: C**

   Liraglutide is dosed once daily; albiglutide and dulaglutide are dosed once weekly. Exenatide is available in 2 different formulations: a once-weekly, long-acting form and a twice-daily form.

6. Which glucagon-like peptide-1 receptor agonist must be reconstituted before administration?

   A. Exenatide twice daily
   B. Albiglutide
   C. Dulaglutide
   D. Liraglutide
Correct Answer: B
Albiglutide must be reconstituted before use. Only the long-acting release form (not the twice-daily form) of exenatide requires reconstitution, and dulaglutide and liraglutide do not require reconstitution.

7. Which of the glucagon-like peptide-1 receptor agonists should be avoided in patients with a creatinine clearance lower than 30 mL/min?

A. Dulaglutide
B. Albiglutide
C. Exenatide***
D. Liraglutide

Correct Answer: C
Dulaglutide, albiglutide, and liraglutide require caution in patients with renal impairment, but no dosing adjustments are recommended. Exenatide should be avoided in patients with a creatinine clearance of 30 mL/min or lower, according to the package insert.

8. Which glucagon-like peptide-1 receptor agonist has been compared to preprandial insulin in head-to-head trials?

A. Lixisenatide
B. Exenatide
C. Albiglutide
D. All of the above***

Correct Answer: D
All of these agents have been compared to preprandial insulin in head-to-head trials.

9. Which of the following is/are an advantage(s) of adding a glucagon-like peptide-1 receptor agonist to insulin?

A. Decreased insulin requirements
B. Less hypoglycemia
C. Weight loss
D. All of the above***

Correct Answer: D
All of the answers are appropriate reasons to use a glucagon-like peptide-1 receptor agonist with insulin.

10. Which of the following patients would be the best candidate for the addition of a glucagon-like peptide-1 receptor agonist?

A. A 17-year-old male with type 1 diabetes and uncontrolled postprandial glucose
B. A 42-year-old female who is normal weight and newly diagnosed with type 2 diabetes
C. An overweight 53-year-old man on metformin with type 2 diabetes and uncontrolled postprandial glucose***

D. An overweight 62-year-old female with type 2 diabetes on 10 units daily of insulin glargine and uncontrolled fasting blood sugar

Correct Answer: C
A is incorrect because glucagon-like peptide-1 (GLP-1) receptor agonists are not approved for type 1 diabetes. B is incorrect because, although a GLP-1 receptor agonist is an option, metformin would be preferred, since it is considered first-line therapy, unless it is contraindicated or not tolerated. D is incorrect because fasting blood sugar should be controlled first; GLP-1 receptor agonists primarily target postprandial glucose levels. Also, the patient is on a minimal dose of insulin glargine, so titrating the insulin glargine would be a better option at this point. C is correct because the patient is overweight and has elevated postprandial glucose. This would be the BEST patient for whom to choose a GLP-1 receptor agonist.