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Solving Clinical Conundrums with Incretin-Based Therapy in Type 2 Diabetes

Mansur E. Shomali, MD
Clinical Associate Professor of Medicine
Division of Endocrinology
University of Maryland School of Medicine
Diabetes and Endocrine Center
Union Memorial Hospital
Baltimore, Maryland

Scott Urquhart, PA-C
Adjunct Clinical Professor
James Madison University PA Program
Clinical Instructor
George Washington University PA Program
Diabetes and Thyroid Associates
Fredericksburg, Virginia

LEARNING OBJECTIVES

After completing this program, the physician assistant/nurse practitioner should be able to:

1. List the benefits and limitations of incretin-based therapies
2. Differentiate the clinical effects of glucagon-like peptide-1 receptor agonists and dipeptidyl peptidase-4 inhibitors
3. Identify strategies for handling real-world challenges when managing patients with type 2 diabetes mellitus using incretin-based therapy

TARGET AUDIENCE:

Nurse practitioners and physician assistants with an interest in the management of patients with type 2 diabetes mellitus.

SPONSOR DISCLOSURE STATEMENT:

Scott Urquhart, PA-C, discloses he is on the Sanofi peer review advisory board.

Mansur Shomali, MD, discloses he serves as medical director for Well Doc, Inc., a technology company that designs medical software applications.

Illinois Academy of Family Physicians/Family Practice Education Network staff disclose that they have no conflicts of interest to report.

Primary Care Metabolic Group staff disclose that they have no conflicts of interest to report.

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ROLE OF THE INCRETIN SYSTEM IN GLUCOSE HOMEOSTASIS

The existence of the incretin system in glucose homeostasis dates back nearly 50 years when it was observed that glucose administered orally produced a greater insulin response than glucose administered intravenously.[1,2] This observation led to the identification of the gut peptide hormones glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide-1 (GLP-1), whichare primarily responsible for the insulinotropic response with oral ingestion of carbohydrates. In persons with type 2 diabetes mellitus (T2DM), the insulino-tropic activity of GLP-1 is preserved, but that of GIP is greatly diminished. As a consequence, the overall insulinotropic response of the incretin system is reduced in persons with T2DM.[3] Further investigation found that administration of GLP-1 augmented the physiologic level of GLP-1 in persons with T2DM, resulting in a decrease in fasting and postprandial glucose levels.[4] It has been determined that GLP-1 exerts its effects on blood glucose by increasing insulin biosynthesis and its release in a glucose-dependent manner,[5-8] inhibiting glucagon secretion in a glucose-dependent manner,[5-9] slowing the gastric emptying rate,[10,11] and promoting satiety.[11-13] In addition to being found in pancreatic islet cells, the GLP-1 receptor (GLP-1R) is found in the stomach, heart, and hypothalamus.[14]

GLP-1 is, however, rapidly inactivated in vivo by the enzyme dipeptidyl peptidase-4 (DPP-4); this has led 2 approaches to overcome the rapid inactivation of endogenous GLP-1.[15] First, GLP-1R agonists have been developed that are resistant to the enzymatic action of DPP-4 and act directly on the GLP-1R. Administration of a GLP-1R agonist achieves a circulating concentration of active GLP-1 equivalent to approximately 60 pmol/L.[16] The GLP-1R agonists currently available in the United States are exenatide for twice-daily administration (exenatide BID), exenatide for once-weekly administration (exenatide QW), and liraglutide for once-daily administration. The other approach to overcome the rapid inactivation of GLP-1 has been the development of agents that block the action of DPP-4, thereby raising the physiologic level of endogenous GLP-1 to approximately 10 pmol/L.[17] The DPP-4 inhibitors currently available are linagliptin, saxagliptin, and sitagliptin.

DISCLOSURES

Dr Shomali reports that he serves as a medical director for, and has stock options from, WellDoc, Inc, a technology company that designs medical software applications. WellDoc, Inc does not have any bias for any pharmaceutical product.

Mr Urquhart reports that he is on the peer review advisory board for Sanofi.

CLINICAL PHARMACOLOGY OF INCRETIN-BASED THERAPY

Glucose lowering

Among the clinical differences within the 2 classes of incretin-based therapy, the glucose-lowering efficacy is greater with the GLP-1R agonists, compared with the DPP-4 inhibitors. This is thought to be due to the direct action of the GLP-1R agonists on the GLP-1R versus the indirect action of the DPP-4 inhibitors. Monotherapy trials generally show that the GLP-1R agonists reduce the A1C level by 0.5% to 1.5%[18-23] and the DPP-4 inhibitors by 0.5% to 0.9%.[24-29] When added to the combination of lifestyle intervention and metformin, the addition of a GLP-1R agonist or DPP-4 inhibitor generally results in similar or slightly greater A1C reductions, compared with monotherapy with a GLP-1R agonist or DPP-4 inhibitor.[9,30-40] The A1C reduction is generally greater in patients with a high A1C. Exenatide BID 10 mcg twice daily for 26 weeks lowered the A1C 0.8% in all patients (mean baseline A1C level, 8.1%), while those with a baseline A1C level ≥10.0% achieved a decrease of 1.2%.[30] For patients with a baseline A1C of 8.2%, liraglutide 1.8 mg once daily for 26 weeks resulted in a reduction of the A1C level of 1.1%, compared with 2.4% in those with a baseline A1C level ≥10.0%.[9] Sitagliptin 100 mg once daily for 24 weeks lowered the A1C level 0.6% for those with a baseline A1C <8.0%, 0.8% for those with a baseline A1C of 8.0% to 8.9%, and 1.5% for those with a baseline A1C ≥9.0%.[25] Linagliptin 5 mg once daily for 24 weeks lowered the A1C level 0.7% from baseline in all patients, compared with 1.0% in patients with a baseline A1C ≥9.0%.[29]

Nonglycemic effects

Effects on nonglycemic parameters, such as body weight, lipids, and blood pressure (BP), are also important considerations when individualizing glucose-lowering therapy for patients with T2DM. Most patients treated with a GLP-1R agonist lose 1 kg to 4 kg.[18-22,41] Patients treated with a DPP-4 inhibitor generally have a slight increase or decrease in body weight, which is considered a weight-neutral effect.[24-26,28,29] The amount of weight lost with a GLP-1R agonist may increase in patients with higher body mass index.[42] The weight loss–promoting effect of the GLP-1R agonists is likely due to a reduction in caloric intake by promoting satiety, and possibly delaying gastric emptying.[4,13,43] A 6-week crossover study showed that exenatide BID reduced caloric intake by 134 kcal following a standardized meal, while caloric intake increased 130 kcal with sitagliptin.[11] Both exenatide and liraglutide have been shown to reduce fat body mass more than lean body mass.[43-47]

TABLE 1 **Adverse events of GLP-1R agonists and DPP-4 inhibitors with an incidence of at least 5% and more frequently than placebo/comparator.**[59-64]

	Adverse events
GLP-1R agonists	
Exenatide BID	Nausea, hypoglycemia, vomiting, diarrhea, feeling jittery, dizziness, headache, dyspepsia, constipation, asthenia
Exenatide QW	Nausea, diarrhea, headache, vomiting, constipation, injection site pruritus, injection site nodule, dyspepsia
Liraglutide	Headache, nausea, diarrhea, anti-liraglutide antibody formation
DPP-4 inhibitors	
Linagliptin	Nasopharyngitis
Saxagliptin	Upper respiratory tract infection, urinary tract infection, headache
Sitagliptin	Upper respiratory tract infection, nasopharyngitis, headache

BID, twice per day; DPP-4, dipeptidyl peptidase-4; GLP-1R, glucagon-like peptide-1 receptor; QW, once weekly.

Effects on BP and lipids are relatively modest. The GLP-1R agonists are generally associated with a 1 to 7 mm Hg reduction in systolic BP, but have no significant effect on diastolic BP.[9,18,20,21,34,48-54] Most studies involving a DPP-4 inhibitor have shown a minimal effect on BP.[34,40,48,55] However, a recent study involving sitagliptin showed a 10 mm Hg reduction in systolic BP over 6 months.[56] With respect to the lipid profile, the greatest effect of the GLP-1R agonists and DPP-4 inhibitors is on the triglyceride level, although some improvement in the low-density lipoprotein cholesterol and high-density lipoprotein cholesterol levels may be observed. A reduction in the triglyceride level of 12 to 40 mg/dL has been observed with the GLP-1R agonists, while an increase of 16 mg/dL to a decrease of 35 mg/dL has been observed with the DPP-4 inhibitors.[9,20,21,26,41,48,50-55,57]

Adverse events and safety

The GLP-1R agonists and DPP-4 inhibitors are generally considered safe and well tolerated with a side effect profile that may be an improvement over some other glucose-lowering therapies.[58] Common adverse events are listed in **TABLE 1**.[59-64] While common with most glucose-lowering agents, hypoglycemia is infrequent with GLP-1R agonist and DPP-4 inhibitor monotherapy, occurring less frequently than with the sulfonylureas or meglitinides.[58] However, when they are combined with a sulfonylurea, the frequency and severity of hypoglycemia are increased.[65-71] Consequently, reducing the dose of the sulfonylurea is recommended with close monitoring when used in combination with a GLP-1R agonist or DPP-4 inhibitor. Other adverse events such as nausea and vomiting with the GLP-1R agonists, as well as long-term safety, are discussed below.

The use of the GLP-1R agonists and DPP-4 inhibitors in patients with kidney dysfunction or who are pregnant, lactating, or elderly may require caution or dose modification (**TABLE 2**).[59-64]

SOLVING CLINICAL CONUNDRUMS

The clinical use of incretin-based therapy requires selecting the agent that best meets a patient's needs and capabilities, with subsequent modification as needed. The following are suggestions to address common conundrums faced in managing patients with T2DM with incretin-based therapy.

Why not initiate incretin-based therapy early in the management of patients with T2DM?

Incretin-based therapy can be initiated early in the management of patients with T2DM, as all 6 incretin-based agents are indicated as an "adjunct to diet and exercise to improve glycemic control in adults with T2DM."[59-64] Of course, metformin remains the recommended initial pharmacologic therapy for most patients with T2DM because of its many benefits and few limitations.[58,72] However, should there be a contraindication or patient intolerance to metformin, any of the other classes of glucose-lowering agents is an option based upon patient characteristics or special issues. Should the avoidance of hypoglycemia be a concern, a GLP-1R agonist, DPP-4 inhibitor, or thiazolidinedione would be the preferred choices. Should the avoidance of weight gain be a concern, a GLP-1R agonist or DPP-4 inhibitor would be the preferred choices.[73]

Instead of using a GLP-1R agonist, why not use insulin?

Insulin is clearly the most effective glucose-lowering agent available and, along with a sulfonylurea, thiazolidinedione, DPP-4 inhibitor, or GLP-1R agonist, is a recommended option for use in combination

TABLE 2 Use of GLP-1R agonists and DPP-4 inhibitors in special populations

	Kidney Dysfunction/↓CrCl	Pregnancy	Lactation/breast feeding	Elderly
GLP-1R agonists				
Exenatide BID	<30: Contraindicated 30-50: Caution 50-80: No dose change	Category C	Discontinue breast feeding or discontinue GLP-1R agonist	No impact of age on safety or effectiveness; use caution
Exenatide QW				
Liraglutide	Use with caution; no dose change			No impact of age on safety or effectiveness
DPP-4 inhibitors				
Linagliptin	No dose change	Category B	Caution	No impact of age on safety or effectiveness; no dose change
Saxagliptin	≤50: 2.5 mg QD >50: No dose change			No impact of age on safety or effectiveness; use caution
Sitagliptin	<30: 25 mg QD 30-49: 50 mg QD ≥50: No dose change			

BID, twice per day; CrCl, creatinine clearance mL/min; DPP-4, dipeptidyl peptidase-4; GLP-1R, glucagon-like peptide-1 receptor; QD, once daily; QW, once weekly.

with metformin and lifestyle management.[72] The benefits of insulin therapy can be limited by frequent hypoglycemia and weight gain, as well as the need for self-injection and frequent self-monitoring of blood glucose. While the A1C-lowering capacity of a GLP-1R agonist is 0.5% to 1.5%, which is less than with insulin, and the GLP-1R agonists require subcutaneous injection, they have important advantages, compared with insulin. These include a low incidence of hypoglycemia and rare occurrence of major hypoglycemia, and, as noted earlier, the GLP-1R agonists promote weight loss. Thus, for patients in whom hypoglycemia is a primary concern or weight loss is especially important, the addition of a GLP-1R agonist may be a good alternative to insulin.[73]

How do I choose among the GLP-1R agonists and DPP-4 inhibitors?

The results of 8 trials comparing one incretin-based agent with another provide a good understanding of the similarities and differences among these 6 agents. The following are some of the significant findings from these studies[9,11,34,48,49,74-76]:

Glucose-lowering effects

- A1C
  - –Liraglutide > exenatide BID[9,49]
  - –Exenatide QW > sitagliptin[34]
  - –Liraglutide > sitagliptin[48,74]
  - –Sitagliptin = saxagliptin[76]
- Fasting plasma glucose
  - –Liraglutide > exenatide BID[9,49]
  - –Exenatide BID = sitagliptin[75]
  - –Exenatide QW > sitagliptin[34]
  - –Liraglutide > sitagliptin[48,74]
  - –Sitagliptin = saxagliptin[76]
- Postprandial glucose
  - –Exenatide BID > sitagliptin[75]

Weight loss

- Exenatide BID = liraglutide[9,49]
- Exenatide BID > sitagliptin[75]
- Exenatide QW > sitagliptin[34]
- Liraglutide > sitagliptin[48,74]
- Sitagliptin = saxagliptin[76]

Low rates of minor hypoglycemia with each of the GLP-1R agonists and DPP-4 inhibitors were observed in these 8 clinical trials. In addition, there were only a few episodes of major hypoglycemia (requiring third-party assistance).

What is known about the long-term safety of the incretin-based therapies? What should I tell my patients?

Clinical trials and postmarketing reports have identified various potential safety issues that are being actively investigated. Pancreatitis has been reported with each of the incretin-based therapies, but a clear

TABLE 3 **Selected FDA-mandated ongoing safety investigations**

Safety issue	GLP-1R agonists			DPP-4 inhibitors		
	Exenatide BID	Exenatide QW	Liraglutide	Linagliptin	Saxagliptin	Sitagliptin
Acute pancreatitis	✔	✔	✔	✔	✔	✔
Thyroid cancer	✔	✔	✔			
Pancreatic cancer	✔	✔				
Cancer, other				✔		
Biliary function	✔					
Cardiovascular		✔	✔	✔	✔	
Renal safety	✔	✔	✔		✔	
Hypersensitivity reaction				✔	✔	
Hepatic events					✔	
Bone fracture					✔	

BID, twice per day; DPP-4, dipeptidyl peptidase-4; FDA, US Food and Drug Administration; GLP-1R, glucagon-like peptide-1 receptor; QW, once weekly.

association has not been established, in part because persons with T2DM have a nearly 3-fold higher incidence of pancreatitis than normoglycemic control.[77] Additionally, a claims-based study involving 88 000 patients showed a similar risk of pancreatitis with exenatide or sitagliptin as with metformin or glyburide.[78] Until the results of ongoing studies and surveillance studies have been completed, it may be best to avoid incretin-based therapy in patients with a history of pancreatitis.

With respect to the GLP-1R agonists, postmarketing reports and rodent studies suggested that these agents might cause medullary thyroid cancer (MTC). Further studies with liraglutide have revealed a small increase in the calcitonin level, a biomarker for MTC, but one that is still within the normal range.[79] Another investigation suggests that C-cell hyperplasia in mice and rats may result from a GLP-1R–mediated mechanism, since exposure to liraglutide at 60 times the human dose for 20 months did not cause MTC in monkeys.[80] The US Food and Drug Administration (FDA) has mandated ongoing studies and a 15-year cancer registry for exenatide QW and liraglutide. During the FDA review of liraglutide, saxagliptin, and linagliptin, new standards regarding cardiovascular safety for all new antidiabetic drugs were adopted. Based on these new standards, the possibility of adverse cardiovascular events with liraglutide, saxagliptin, and linagliptin could not be definitively ruled out. Additional clinical trials to better assess the potential for cardiovascular risk with these 3 agents are ongoing.

Other safety investigations involving each of the GLP-1R agonists and DPP-4 inhibitors are under way (**TABLE 3**).[81-86] These investigations should identify any safety concerns much sooner than relying on postmarketing reports.

What are the recommendations for blood glucose monitoring with incretin-based therapy?

Current recommendations by the American Diabetes Association/European Association for the Study of Diabetes and American Association of Clinical Endocrinologists/American College of Endocrinology provide no specific advice regarding self-monitoring of blood glucose for patients using incretin-based therapy. In addition, the approved product labeling for the 6 incretin-based therapies only indicate that "patients should also be informed about the importance of ... periodic blood glucose monitoring and A1C testing..."[59-64] Since a key role for blood glucose monitoring is to reduce the risk of or identify hypoglycemic episodes, and the incidence of minor hypoglycemia is low and major hypoglycemia rare with incretin-based therapies, regular self-monitoring of blood glucose seems unnecessary. However, should incretin-based therapy be used in combination with a secretagogue or insulin, more frequent monitoring of blood glucose is recommended. Patients should be educated about the signs and symptoms of hypoglycemia, proper treatment of low blood sugars, and ways in which to minimize future hypoglycemic episodes.

What strategies can be employed to minimize the risk of nausea/vomiting with a GLP-1R agonist?

Early clinical trials showed that nausea and/or vomit-

ing was commonly experienced by patients treated with a GLP-1R agonist. Subsequent clinical trials initiated treatment with exenatide BID and liraglutide using a dose escalation strategy, resulting in a lower incidence of nausea and vomiting.[9] The recommended dose escalation strategies are as follows: Exenatide BID should be initiated at a dose of 5 mcg twice daily and taken within 60 minutes before the morning and evening meals. The dose of exenatide BID can be increased to 10 mcg twice daily after 1 month, based on glycemic response.[59] Liraglutide should be initiated at a dose of 0.6 mg once daily for 1 week, then increased to 1.2 mg once daily. If acceptable glycemic control is not achieved at a daily dose of 1.2 mg, the dose of liraglutide can be increased to 1.8 mg once daily. Liraglutide can be taken independent of meals.[61] Exenatide QW is initiated at a dose of 2 mg once weekly without dose escalation at any time of the day and without regard to meals.[60]

Other strategies that can be employed to minimize the risk of nausea and/or vomiting with GLP-1R agonist therapy include lengthening the time period over which dose, escalation is achieved; temporarily reducing the dose should nausea and/or vomiting occur; taking exenatide closer to mealtime than 1 hour; and stopping eating upon feeling full.[87-89] Another recommendation is to have patients eat one-quarter to one-third less of their usual total food volume at all meals. This will prevent them from feeling bloated or full, which may be the cause of nausea and gastrointestinal discomfort.

What strategies do you suggest to address patient barriers and improve adherence with incretin-based therapy?

The generally complex nature of patient adherence requires a multifaceted approach to improve it. Health care providers and their ancillary support staff can be instrumental in improving patient adherence and promoting self-management. Elements of this multifaceted approach include fostering a collaborative relationship with the patient, individualizing and modifying therapy as needed, and providing ongoing education and support to foster patient self-management.[90] Setting goals based on the patient's situation (eg, life expectancy, social situation) and simplifying the treatment regimen are also essential.[90,91]

Recommendations to improve adherence with incretin-based therapy include identifying and resolving specific patient concerns. Reviewing the benefits of these agents, particularly weight effects and the low incidence of hypoglycemia, can contribute to patient self-motivation. Needle phobia with the GLP-1R agonists, if present, can often be overcome by having the patient self-inject in the office using the appropriate pen/device. Discussing cost concerns and determining insurance coverage are especially important. Prescription assistance programs through manufacturers or the state can also be helpful. ■

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