

GLP-1 receptor agonists in the management of Type 2 Diabetes

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Abstract

Despite advances in options for the treatment of type 2 diabetes, optimal glycaemic control is often not achieved. Hypoglycaemia and weight gain associated with many antidiabetic medications may interfere with the implementation and long-term application of treatment strategies. Glucose homeostasis is dependent on a complex interplay of multiple hormones and gastrointestinal peptides, including glucagon-like peptide-1 (GLP-1). Abnormal regulation of these substances may contribute to the clinical presentation of diabetes. GLP-1-based therapies affect glucose control without causing hypoglycaemia through several mechanisms, including enhancement of glucose-dependent insulin secretion, slowed gastric emptying, regulation of postprandial glucagon, and reduction of food intake.

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Introduction

The management of patients with type 2 diabetes mellitus (diabetes) is becoming increasingly complex.¹ The focus of treatment has been on increasing insulin availability, either through direct insulin administration or through oral agents that promote insulin secretion or improve sensitivity to insulin, or on delaying the delivery and absorption of carbohydrate from the gastrointestinal tract.² Although the use of metformin has been the initial therapy for most patients, the progressive nature of type 2 diabetes implies that pharmacological agents, in addition to metformin, are required for glycaemic control.¹

Incretin-based therapies represent a therapeutic class with which to achieve treatment goals of type 2 diabetes.³ Incretin-based therapies consist of two classes: (1) glucagon-like peptide 1 (GLP-1) receptor agonists, which act solely on the GLP-1 receptor and (2) dipeptidyl-peptidase-4 inhibitors (DPP-4 inhibitors) available as oral medications, which raise endogenous GLP-1 and other hormone levels by inhibiting the enzyme DPP-4.⁴ The focus of this article will be to review the actions and appropriate place in therapy for the GLP-1 receptor agonists, exenatide and liraglutide.

Incretin-based therapy

Incretins are hormones found in the gut that are secreted from enteroendocrine cells into the blood within minutes after eating. One of their many roles is to increase insulin secretion and suppress glucagon secretion from the beta (β) and alpha (α) cells of the pancreas, respectively, after eating. The net effect is

to increase insulin-mediated glucose uptake in peripheral tissues and to suppress hepatic glucose production, both of which result in the lowering of blood glucose.⁵

The incretin effect

According to the incretin effect, oral glucose has a greater stimulatory effect on insulin secretion than intravenous glucose. This is mediated by several gastrointestinal peptides, particularly GLP-1. GLP-1 also suppresses glucagon production and, in pharmacological doses, can delay gastric emptying and reduce food intake.⁵

GLP-1 agonists

GLP-1 levels are abnormally low in patients with type 2 diabetes. Endogenous GLP-1 has a short half-life of one to two minutes, as a result of rapid degradation by the enzyme DPP-4. GLP-1 levels can be raised therapeutically by the use of injectable GLP-1 receptor agonists that are resistant to enzymatic degradation, or by an oral DPP-4 inhibitor (DPP-4i). When used as monotherapy, these agents do not cause hypoglycaemia because the effect on insulin and glucagon secretion is glucose-dependent.⁵

GLP-1 receptor agonists work by binding to GLP-1 receptors located throughout the body, especially on pancreatic α and β cells. An injection of a GLP-1 receptor agonist "floods" the binding sites of the receptors to a much greater degree than the DPP-4 inhibitors; thus, these drugs tend to reduce blood glucose levels, reduce weight, slow gastric emptying, and lower glucagon levels

more substantially than DPP-4 inhibitors.³ GLP-1 receptor agonists are an attractive choice for patients in whom promotion of weight loss is a major consideration and the level of blood glucose control (HbA_{1c}) is moderately elevated (8.0%) and where insulin is not required.³ The two GLP-1 receptor agonists currently available in South Africa are exenatide and liraglutide.⁶ The GLP-1 agonists are available only as injectables in the form of pen devices.⁵ These agents are not to be used in the treatment of type 1 diabetes.⁶

The management of type 2 diabetes

Diabetes requires the medical management of each patient to be approached comprehensively, based on the patient's unique medical history and risk factors, behaviours, and ethnocultural background and environment. Glucose targets should be individualised and should take into account the patient's age, duration of disease, presence or absence of microvascular complications, presence or absence of macrovascular disease (including risk factors for cardiovascular disease [CVD]), and risk for severe hypoglycaemia. The usual target of HbA_{1c} levels for patients with type 2 diabetes remains less than 7%. For all patients with type 2 diabetes, CVD risk reduction is important. For lipids, the primary goal is to reduce low density lipoprotein cholesterol (LDL-C) in patients with or without coronary artery disease. One of the most important goals in the management of type 2 diabetes is weight loss of 5 to 10% of body weight which provides benefits in improving hyperglycaemia, dyslipidaemia and hypertension. Medical nutrition therapy continues to be the cornerstone of efforts to improve outcomes for patients with type 2 diabetes. Patients should be encouraged to moderate calorie and carbohydrate intake, reduce saturated fat and increase fibre intake. Since lifestyle interventions alone may not achieve or maintain HbA_{1c} goals, concurrent treatment with metformin, sulphonylureas (SU), insulin, thiazolidinediones (glitazones) or incretin-based therapies may be required.³

Exenatide

Exenatide (Byetta®) is indicated as add-on therapy for patients with type 2 diabetes mellitus inadequately controlled by lifestyle modification and other oral antidiabetic therapy.^{6,7} Exenatide is a short-acting GLP-1 receptor agonist available in 5 µg and 10 µg pens and is administered twice a day before meals.^{3,5} The primary effect of short-acting GLP-1 receptor agonists such as exenatide is the lowering of post-prandial glucose levels.³

Liraglutide

Liraglutide (Victoza®) is indicated as an adjunct to diet and exercise to achieve glycaemic control in type 2 diabetes.⁶ This long-acting GLP-1 receptor agonist is administered subcutaneously once a day.

Both exenatide and liraglutide are associated with weight loss. However, weight loss is more profound in patients with greater starting body mass indices. GLP-1 receptor agonists also have

beneficial effects on blood pressure and significant improvements in very low-density lipoprotein (VLDL), free fatty acids, and triglycerides.³

Place in therapy

A treatment algorithm has been developed by the Society for Endocrinology, Metabolism and Diabetes of South Africa (SEMDSA) for the clinical use of GLP-1 receptor agonists. The formulation of the current guideline has taken into consideration the challenge that type 2 diabetes is not a homogenous disease and is poorly managed, with less than 50% of patients achieving glycaemic targets. The aim of therapy is to achieve and maintain the HbA_{1c} below the patient's individualised target level.⁵

The newer incretin-based therapies, including GLP-1 receptor agonists, have been included as part of the diabetes treatment algorithm due to their efficacy without the burden of weight gain and hypoglycaemia.

The following criteria must be met for add-on therapy with a GLP-1 receptor agonist as part of a three-drug regimen:⁵

- Inadequate glycaemic control on combination therapy with maximally-tolerated doses of metformin and a sulphonylurea (SU), and
- Patient is not a candidate for a third oral agent, and
- Patient is a poor candidate for insulin therapy, and
- Reduction in HbA_{1c} less than 1.5% is required in order to reach the patient-specific HbA_{1c} goal.

The following criteria must be met for add-on therapy as part of a two-drug regimen:⁵

- Patient has not achieved desired HbA_{1c} with one oral agent and is not a candidate for any other agent (oral or insulin) available, and
- Reduction in HbA_{1c} less than 1.5% is required in order to reach the patient-specific HbA_{1c} goal.

The main advantage is that, unlike most other antidiabetic agents used in type 2 diabetes, the GLP-1 receptor agonists promote weight loss. According to a study which compared liraglutide 1.8 mg with exenatide 10 µg twice daily in patients inadequately controlled on metformin and/ or a sulphonylurea, the mean weight loss over 26 weeks was 3 kg.⁵

Safety

While the GLP-1 receptor agonists do not cause hypoglycaemia on their own, the risk is increased when used in combination with other agents associated with hypoglycaemia, such as the sulphonylureas. It is recommended to reduce the sulphonylurea dose when adding a GLP-1 receptor agonist.⁵

The most common adverse effects of the GLP-1 agonists are those related to the gastrointestinal tract namely, nausea and vomiting, which may occur on initiating therapy.^{3,5} Although this can be severe and may lead to discontinuation of therapy, nausea is

Table 1: 2012 SEMDSA treatment algorithm for type 2 diabetes⁵

2012 SEMDSA treatment algorithm for type 2 diabetes					
Algorithm to be used only if the patient does not have features of severe decompensation. ^a					
Progress down this algorithm within three months if HbA _{1c} remains above 7% (or above the individualised target).					
Choose therapies that are likely to produce the HbA _{1c} reduction required to achieve the target.					
Do not proceed with drug therapy without annual serum Glomerular Filtration Rate (GFR) measurement.					
Lifestyle measures plus	Preferred therapies		Alternate therapies for special circumstances		
Step 1: Initiate at least one oral drug at diagnosis	Metformin		Sulphonylurea	DPP-4i	Acarbose
↓	↓		↓		
Step 2: Combine any two drugs ^b	Metformin	Sulphonylurea (SU)	Incretin-based therapy	Acarbose	Basal insulin
↓	↓		↓		
Step 3: Combine three drugs	Metformin + SU + basal insulin (or metformin + pre-mix insulin)		Metformin + SU + Incretin-based therapy		Metformin + SU + Acarbose
↓	↓		↓		
Step 4: More advanced therapies	Refer to specialist for basal + mealtime insulin ± metformin ± acarbose ± incretin therapy		Metformin + pre-mix Insulin (if not used yet)		

^aSevere decompensation includes any of the fasting plasma glucose > 15 mmol/l, HbA_{1c} >11%, marked polyuria and polydipsia, weight loss > 5% or ketoacidosis. Refer patient for specialist care (Step 4).

^bIf, at diagnosis, the patient's HbA_{1c} is > 9% without features of severe decompensation, consider initiating therapy at Step 2.

usually transient, usually lasting between four to eight weeks and can be minimised by up-titrating the dose slowly. Symptomatic relief can be achieved with the use of anti-nausea medication.⁵ Patients should be advised that eating beyond satiety may trigger nausea when using a GLP-1 receptor agonist.³

There have been reports of pancreatitis with use of GLP-1 receptor agonists. Patients should be warned to report symptoms suggestive of pancreatitis immediately, to discontinue the drug immediately on suspicion of pancreatitis and not to restart a GLP-1 agonist if the diagnosis of pancreatitis is confirmed.⁵

Contraindications

The use of GLP-1 receptor agonists is contraindicated in the following circumstances:⁵

- There is a compelling indication for insulin therapy
- History of hypersensitivity
- Renal failure
- Personal or family history of medullary thyroid carcinoma (MTC) or multiple endocrine neoplasia syndrome (liraglutide only)
- Patient has severe gastrointestinal disease, including gastroparesis
- Patient has a history of pancreatitis
- Triglyceride level >10 mmol per litre, gallstones with intact gallbladder, and alcohol abuse
- Planned treatment regimen includes a DPP-4 inhibitor
- Patient is not obese

Conclusion

GLP-1 receptor agonists represent an exciting addition to the treatment options for patients with type 2 diabetes when used in combination with lifestyle modification or as part of combination therapy strategies.³ These agents have the potential to change the paradigm of diabetes treatment because of improved glycaemic control, freedom from hypoglycaemia, and association with weight loss. Treatment with GLP-1 receptor agonists will target those patients in whom other conventional agents are poorly tolerated or for whom weight loss is more highly prized.⁸

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