The New Kids on the Block: Incretin Therapy for Management of Type 2 Diabetes

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Over the last few years, choices for medical management of type 2 diabetes have increased rapidly. One such option, incretin based therapies, offers a new approach to the management of type 2 diabetes. With a mechanism of action distinct from other existing classes of oral hypoglycemic agents, these agents improve glycemic control by increasing concentrations of GLP-1. GLP-1 is a hormone produced by the gastrointestinal tract in response to oral nutrients. GLP-1 acts to lower glucose following a meal through stimulation of insulin production from the pancreas. In healthy subjects, the GLP-1 effect accounts for 60% of the insulin response. Apart from stimulation of insulin production, GLP-1 has a number of other effects that work to decrease glucose levels. These include delaying gastric emptying, decreasing glucagon production, and suppressing appetite. GLP-1 hormone has a short duration of action and is inactivated in the body through metabolism by the DPP-4 enzyme. In Canada, there are two main pharmacological agents that have incretin action: GLP-1 agonists (liraglutide and exenitide) and DPP-4 inhibitors (sitagliptin and saxagliptin).

Meet Frank

Frank, a 55-year-old accountant presents for management of his type 2 diabetes. He has a sedentary lifestyle and an irregular schedule for meals. He is currently on Metformin 1 g b.i.d., ramipril 10 mg q.d., and hydrochlorothiazide 25 mg per day. He has gained 15 pounds in the last year; his weight is now at 220 lbs, and his BMI is 32 kg/m2. HbA1c is 7.8%. He is worried about continued weight gain and risk of hypoglycemia.

GLP-1 Agonists

Clinical efficacy and safety of liraglutide has been assessed in five phase III, 26 week, multicentre, randomized controlled trials the Liraglutide Effect and Action in Diabetes (LEAD) trials that investigated the effect of liraglutide over a range of different treatment scenarios.[1-5] In these trials, liraglutide was effective in HbA1C lowering of 0.8 to 1.5% alone or in combination with one to two other oral agents. Lower rates of hypoglycemia were observed as were improvements in pancreatic function. Moderate weight loss and reduction of systolic blood pressure were also found. Main side effects were gastrointestinal (GI) in nature, but they were transient. Currently there is no data concerning long-term safety, mortality, diabetic complications, or quality of life in patients with diabetes treated with liraglutide. Liraglutide is currently approved for use as an additional therapy following metformin or metformin and sulfonylurea agents in patients with type 2 diabetes, who have not reached glycemic targets. Liraglutide is administered by subcutaneous injection and is available in pre-filled syringes. Starting dose is 0.6 mg q.d. for one week to reduce GI side effects. After one week, the dose is increased to 1.2 mg q.d. Maximum dose is 1.8 mg q.d..

Exenitide is derived from the saliva of the Gila monster, the largest lizard native to the United States. Gila monster saliva shares a 53% sequence homology with human GLP-1 and is resistant to degredation by the DPP-IV enzyme. Compared to

Table 1

DPP-4 Inhibitors Compared to GLP-1 Inhibitors

	Liraglutide	Exenitide	Saxagliptin	Sitagliptin
Class	Human GLP-1 Analogue	Exendin-based GLP-1 Analogue	DPP-4 Inhibitor	DPP-4 Inhibitor
Administration	Injection (Subcutaneous)	Injection (Subcutaneous)	Oral	Oral
Frequency	Once Daily	Twice Daily	Once Daily	Once Daily
Dosage	Initial: 0.6 mg Maintenance: 1.2 mg Increase to 1.8 mg Based on Clinical Response	Initial 5 ug b.i.d. Increase to 10 ug b.i.d.	5 mg	100 mg
Main Side-Effects	Nausea	Nausea	Nasopharyngitis	Upper Respiratory Tract Infection

liraglutide, exenitide is associated with greater antibody production, but this does not appear to be clinically significant. In randomized controlled trials, exenitide is associated with an additional A1C lowering of 0.5 to 1% when used in combination with either metformin and sulfonylurea or sulfonylurea alone.[6,7] Exenitide is currently approved for use with sulfonylureas, metformin, and thiazolidinediones. It is administered by subcutaneous injection twice per day. Starting dose is 5 ug b.i.d .to a maximum dose of 10 ug b.i.d.

There have been few studies that have compared exenitide to liraglutide. The LEAD 6 study compared exenitide 10 ug b.i.d. to liraglutide 1.8 mg/day.[8] Similar reductions in A1C was observed between the two agents with similar rates of weight loss and nausea.

DPP- 4 Inhibitors

Sitalgliptin and saxagliptin are the DPP-4 inhibitors currently available in Canada. DDP-4 inhibitors inhibit the breakdown of GLP-1, thereby increasing the concentration of endogenous GLP-1 that is secreted in response to food intake. DDP-4 inhibitors have been shown to be effective at lowering HbA1c by approximately 0.5% when used as monotherapy or in combination with either metformin or sulfonylurea agents.[9,10] They are weight neutral and, in general, well tolerated. A meta-analysis of the use of sitagliptin did show an increase in nasopharyngitis and urinary tract infection.[11] As with the GLP-1 agonists, there is no data on long-term safety, mortality, diabetic complications, or quality of life in patients using these agents for treatment of type 2 diabetes. DPP-4 Inhibitors are currently approved for use in patients failing to achieve control on metformin alone. These medications are administered orally as a once per day dose.

Where do they fit in diabetes management?

The incretins are another option for diabetes management as an additional therapy for patients who have not yet achieved glycemic control after metformin therapy (DPP-4 inhibitors and GLP-1 agonists) or metformin and sulfonylurea therapy (GLP-1 agonists). Advantages of these medications are weight loss (GLP-1 agonists) or weight neutrality (DPP-4 inhibitors), good HBA1c lowering ability with

minimal risk of hypoglycaemia when used with metformin. When considering these medications, these advantages have to be balanced with limited long-term data and with the cost of these medications.

Cautions and Contraindications

The main side-effects associated with GLP-1 agonists are nausea and vomiting. These side effects appear to worsen at higher doses. Typically, nausea abates within the first few weeks of therapy. Pancreatitis has been reported in a small number of patients taking both liraglutide and exenitide. Pancreatitis should be suspected in a patient on GLP-1 agonist who presents with severe or persistent abdominal pain. In patients who have had pancreatitis, GLP-1 agonists should be discontinued and not restarted. In rats and mice, exposure to liraglutide has resulted in c-cell stimulation, but no evidence of such an effect has been seen in humans. However, because of this animal data, liraglutide is contraindicated in patients with a personal or family history of medullary thyroid cancer or MEN 2B. Other contraindications include pregnant patients, those in severe renal failure, and the pediatric population. DPP-IV inhibitors are generally well tolerated. Main side-effects include nasopharyngitis, upper respiratory tract infection, and allergy.

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Table 2
The Incretin Patient

Incretin therapy may be beneficial when:	Choosing between GLP-1 agonist and DPP-IV inhibitors
• A1C is not at target with metformin • Weight gain is a concern • Hypoglycemia is particularly undesireable	• Patient preference (oral versus injection) • Weight neutrality versus weight loss • Cost • A1C lowering (greater with GLP-1 agnosits)

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