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Use of Incretin Therapy in the Treatment of Type 2 Diabetes Mellitus

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ABSTRACT

Glucagon-like peptide-1 receptor agonists and dipeptidyl-peptidase 4 inhibitors are 2 of 6 second-line medication options in diabetes management according to the 2016 American Diabetes Association guidelines. Providers must take many factors into consideration when choosing a treatment regimen, including patient preference, cost and insurance coverage, efficacy, and tolerability. Side effects, such as hypoglycemia and weight gain, often contribute to lack of control and poor adherence. Glucagon-like peptide-1 receptor agonists and dipeptidyl-peptidase 4 inhibitors are well-tolerated options that improve glycemic control with a low incidence of hypoglycemia and weight gain. In this article we review the similarities, differences, advantages, and disadvantages of the incretin therapies.

Keywords: GLP-1 receptor agonists, DPP-4 inhibitors, incretin therapy, primary care, type 2 diabetes mellitus

INTRODUCTION

Based on the 2014 National Diabetes Statistics report, 29.1 million, or 9.3%, of Americans were living with type 2 diabetes mellitus in 2012 and another 1.4 million were diagnosed.[1] Diabetes is becoming increasingly more financially burdensome; the American Diabetes Association (ADA) estimated that the cost associated with diabetes was $245 billion in 2012, $176 billion of which was spent on medically related costs and the remaining $69 billion on reduced productivity.[2] This is a 40% increase from just 5 years earlier.[2] Metformin and lifestyle modifications—diet and exercise—remain the mainstay of initial treatment, but they are often not enough to achieve target hemoglobin A_{1c} (A_{1c}) levels. If this is the case, or if there are contraindications to metformin, then addition of a second agent is recommended.[3] The ADA currently recommends the following, in order of preference, as second-line options: glucagon-like peptide-1 receptor agonists (GLP-1 RA); sodium-glucose cotransporter-2 inhibitors; dipeptidyl-peptidase 4 (DPP-4 inhibitors); thiazolidinediones; α-glucosidase inhibitors; sulfonylureas; and basal insulin (with an initial $A_{1c} \geq 7.5\%$).[3] Providers must consider many factors when formulating a diabetes treatment plan, such as patient preference, cost and insurance coverage, efficacy, and tolerability. Side effects like hypoglycemia and weight gain often contribute to lack of control and poor adherence. GLP-1 RA and DPP-4 inhibitors are well-tolerated options that improve glycemic control with a low incidence of hypoglycemia and weight gain. In this article we review the similarities, differences, advantages, and disadvantages of these incretin therapies.

PHARMACOLOGIC: MECHANISM OF ACTION

Type 2 diabetes mellitus is characterized by elevated blood glucose in the setting of relative insulin deficiency. Both genetic predisposition and environmental factors, mainly obesity and a sedentary lifestyle, result in insulin resistance, dysfunction in insulin release by pancreatic β cells, and an increase in hepatic glucose production.[4] These factors all contribute to hyperglycemia, despite the fact that insulin levels may be normal or even elevated in type 2 diabetes.[4] Insulin resistance results in decreased glucose uptake by muscle, liver, and fat cells.[4] In

addition, insulin resistance induces β cells to secrete more insulin, which leads to their deterioration over time, and impaired insulin secretion.[4]

In the past 10-15 years the incretin mimetics, DPP-4 inhibitors and GLP-1 RA, have come onto the market as novel forms of treatment for type 2 diabetes. Incretins are proglucagon hormones produced by the L cells of the small intestine.[4] They stimulate insulin secretion by the pancreatic β cell and are released into the bloodstream by the gastrointestinal (GI) system in response to nutrients, mainly glucose and carbohydrates.[4] GLP-1 only has a half-life of 1.5 minutes, is quickly degraded by the DPP-4 enzyme, then cleared by the kidney.[5] Consequently, GLP-1 cannot be used therapeutically in its natural state. As a result, approaches to treatment have addressed development of derivatives that avoid renal clearance and enzymatic degradation, which require these drugs to be administered subcutaneously.[6]

The incretin therapies activate pancreatic β-cell secretion of insulin exclusively in the presence of elevated blood sugar. This is an important concept as this contributes to the low incidence of hypoglycemia seen with GLP-1 RA and DPP-4 inhibitors.[6]

DPP-4 Inhibitors

The DPP-4 enzyme enhances endogenous glucose metabolism by increasing endogenous GLP-1. Available drugs in the United States include sitagliptin (Januvia, Merck), saxagliptin (Onglyza, AstraZeneca), linagliptin (Tradjenta, Boehringer Ingelheim), and alogliptin (Nesina, Takeda). The enzyme is expressed on the surface of many cell types. DPP-4 inhibitors are a class of oral medications used to extend the half-life of GLP-1, thereby increasing the level of endogenous GLP-1 and resulting in an increase of insulin and a decrease in blood glucose.[7] The effect on glycemic control of medications in this class is limited when compared with administration of exogenous GLP-1 RA (Table 1).

GLP-1 RA

GLP-1 RA work similarly by increasing β-cell stimulation through the GLP-1 incretin pathway.[6] Their mechanism of action results in a more potent increase in GLP-1 activity compared with DPP-4 inhibitors (Table 1).[6] Available drugs in the US for this class include exenatide (Byetta and Bydureon, AstraZeneca), liraglutide (Victoza, Novo Nordisk), albiglutide (Tanzeum, GSK), and dulaglutide (Trulicity, Eli Lilly). In addition, these agents have

Table 1. Risks/Benefits

	Mechanism of Action	A_{1c} Reduction	Benefits	Risks
DPP-4 inhibitors	Inhibits the DPP-4 enzyme extending the half-life of the incretin hormones. This results in an increase in insulin and a decrease in blood glucose levels.	0.5-0.7%	• Weight neutral • Low risk of hypoglycemia • Coformulations with metformin available • Oral administration	• Hypersensitivity reactions • Heart failure • Pancreatitis • Joint pain • Insurance coverage • Cost
GLP-1 RA	Increases β-cell stimulation resulting in an increase in insulin secretion. Inhibits glucagon release, slows gastric emptying, and enhances satiety.	0.5%-1.5%	• Weight loss 1-4 kg • Reduction in systolic blood pressure 1-7 mm Hg • Improved lipid profile • Low risk of hypoglycemia	• GI side effects • Injection-site reactions • Pancreatitis • Thyroid C-cell cancer • Insurance coverage • Cost

A_{1c} = hemoglobin A_{1c}; DPP-4 = dipeptidyl-peptidase 4 inhibitor; GI = gastrointestinal; GLP-1 RA = peptide-1 receptor agonists.