The Role of the Incretin System in the Treatment of Type 2 Diabetes

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Type 2 diabetes is a major health threat in the United States. The rate of death from heart disease and stroke is two to four times higher in patients with diabetes. Diabetes is also the leading cause of blindness, amputation, and end stage renal disease (ESRD) in the United States. The importance of adequately treating patients with type 2 diabetes cannot be underestimated. Standards of care in patients with type 2 diabetes indicate all patients should be treated to a hemoglobin A1C of less than 7%; however, only 40% of patients with diabetes successfully reach this goal. This highlights the necessity of developing new treatments for patients with type 2 diabetes.

Medications for Type 2 Diabetes

Hyperglycemia in type 2 diabetes is attributable to several factors; typically type 2 diabetes is thought of as a dysfunction of the pancreatic beta cells with a background of insulin resistance. In addition to the aforementioned dysfunction, patients with type 2 diabetes also experience pancreatic alpha cell defects as well as inappropriate hepatic glucose production. In the past, available medications have not targeted all of these sites. The following table lists medications available for treatment of type 2 diabetes prior to the use of incretin related medications:

Medication	Mechanism of Action (MOA)	Adverse Drug Events (ADE)	A1C Decrease	Comments
Metformin	Decrease hepatic glucose production; increase glucose uptake (muscle)	Significant GI upset (cramping and diarrhea) on initiation	1.5-2%	• Modest weight loss • First line therapy according to ADA • Contraindicated in renal impairment and hepatic disease
Sulfonylureas (such as glipizide, glyburide, glimepiride)	Enhance endogenous insulin secretion from pancreatic beta cells	Weight gain, hypoglycemia	1.5-2%	• Lose efficacy over time
Non-sulfonylurea secretagogues Prandin® (repaglinide), Starlix®, (nateglinide)	Enhance endogenous insulin secretion from pancreatic beta cells	Weight gain, hypoglycemia	0.8-1%	• Shorter acting than sulfonylureas • Dosed with meals • Contraindicated in hepatic dysfunction
Insulin	Replaces or supplements endogenous insulin	Weight gain, hypoglycemia hypokalemia	--	• Contraindicated with hypoglycemia and hypokalemia • Requires more careful patient monitoring
Thiazolidinediones (TZDs) Actos® (pioglitazone), Avandia® (rosiglitazone)	Insulin sensitizers; enhance glucose uptake in adipose and muscle tissues	Weight gain, edema, can potentiate CHF exacerbations, increased LDL (rosiglitazone)	1.5%	• Caution with CHF patients • Recent reports of increased risk of MI with rosiglitazone
Alpha glucosidase inhibitors Precose® (acarbose), Glyset® (miglitol)	Block degradation of complex carbohydrates in small intestine	Severe GI symptoms (especially flatulence)	0.3-1%	• Affect post prandial glucose levels • Contraindicated in GI disease/obstruction, IBD, renal failure • Significant drug interactions; administer separately from other drugs

American Diabetes Association (ADA) Treatment Recommendations

The ADA recently released treatment guidelines for patients with type 2 diabetes stating that metformin and lifestyle modifications should be used initially in all patients without contraindications. If A1C goal is not met with metformin monotherapy, then one of three second line agents can be added. Currently, TZDs, sulfonylureas, and insulin are considered second line agents. If a patient's goals are still unmet, then insulin therapy should be initiated or intensified. Several medications are not included in this ADA algorithm; this is because of less impressive reductions in A1C and/or a lack of available trial data at the time of publication.

The Incretin Effect

The incretin system represents a novel treatment pathway for patients with type 2 diabetes. The 'incretin effect' was first identified by administering oral and IV glucose to patients without diabetes and testing insulin levels. It was discovered that there is a huge spike in insulin production in healthy patients receiving oral glucose (three times greater insulin production) compared to IV glucose. This led to the theory of gut hormones responsible for this insulin secretion. The **incretin effect** is defined as the difference in insulin response to oral versus IV glucose loads. Eating promotes the secretion of multiple GI hormones involved in regulation of gut motility and stimulation of insulin secretion. In healthy patients, up to 50% of the post-prandial insulin secretion is the result of the incretin effect.

Two gut hormones have been identified: Glucose dependent insulinotropic hormone (GIP) and glucagon like peptide-1 (GLP-1). Secretion of GLP-1 is impaired in patients with type 2 diabetes. GLP-1, which is secreted in response to nutrients, enhances insulin secretion in a glucose dependent manner, and is produced in L cells of the small intestine. GLP-1 exerts its main effect by stimulating glucose dependent insulin release from pancreatic beta cells. In addition, GLP-1 slows gastric emptying, inhibits inappropriate postmeal glucagon release from the pancreatic alpha cells, and promotes satiety, thereby decreasing food intake.

GLP-1 has a very short half life (plasma half life <1 minute); it is degraded almost immediately by the dipeptidyl peptidase-4 enzyme (DPP-4). Presently, strategies are being aimed at developing GLP-1 analogues and receptor agonists (incretin mimetics) that resist degradation by DPP-4, as well as agents that inhibit DPP-4 resulting in increased levels of endogenous GLP-1.

Current Incretin Treatment Options

There are presently two incretin treatment strategies currently available and several others on the horizon. As mentioned earlier, there are the GLP-1 agents and the DPP-4 inhibitors. Of the GLP-1 agents, only exenatide (Byetta®) is currently available. Exenatide LAR (once weekly dosing) and liraglutide (once daily dosing) are still in development. There are several DPP-4 inhibitors still in clinical trials, including vildagliptin (Galvus®) and saxagliptin. Only sitagliptin (Januvia®) has currently received FDA approval.

Exenatide (Byetta®)

Exenatide (Byetta®) is the first in a new class of incretin mimetics. It enhances glucose dependent insulin secretion, suppresses inappropriately elevated glucagon secretion, and slows gastric emptying. Exenatide is derived from exendin 4, which is found in the salivary gland of the Gila monster. Since it is a synthetic GLP-1 agonist, it resists degradation by DPP-4.

Exenatide is indicated only as an adjunct therapy for treatment of type 2 diabetes. It can be used in combination with metformin, sulfonylureas, TZDs, metformin + TZD, or metformin + sulfonylurea. Exenatide is available as a prefilled pen in a 5 mcg or 10 mcg dosage; each pen delivers 60 doses. Patients will need to purchase pen needles separately. Exenatide is typically administered via subcutaneous injection 60 minutes before morning and evening meals. Therapy is initiated with the 5 mcg dose; titration to the 10 mcg dose can be done after 4 weeks of treatment at the lower dose. Exenatide is predominately renally excreted; therefore, it is not recommended in patients with severe renal impairment. Exenatide is also not recommended in patients with severe gastrointestinal disease due to its gastrointestinal side effects.

Many patients (40%) experience nausea upon initiation of therapy; other common side effects seen in trials are vomiting, diarrhea, jitteriness, headache, and injection site reactions. With continuation of therapy, the GI side effects decrease. Hypoglycemia is not seen when Byetta is combined with metformin; however, when Byetta® is used with the sulfonylureas, the risk of hypoglycemia is increased. Despite the nausea upon therapy initiation, many patients are willing to try Byetta® because of the weight loss seen with this product. In trials of up to 30 weeks, weight loss of up to 3 kg is seen; in longer trials, lasting 82 weeks, average weight loss is 4.4 kg. Patients with larger baseline BMIs (>40) had a greater mean reduction in weight than patients with smaller BMIs (<25); 7 kg of weight loss versus 2 kg, respectively.

Due to Byetta's® effect on gastric emptying, it should be used cautiously with medications requiring rapid GI absorption. Caution patients to take medications such as oral contraceptives and antibiotics at least one hour before a Byetta® injection. There have been some cases of increased INR in warfarin patients using exenatide concomitantly.

Byetta® was approved based on three clinical trials lasting 30 weeks; the trials contained a total of 1446 patients. Byetta® was studied in combination with metformin, sulfonylureas, and metformin + sulfonylurea. When compared to placebo, sustained weight loss was seen in all three studies. Decreases in A1C of 0.8% were seen when exenatide 10 mcg BID was combined with metformin, 0.9% with sulfonylurea, and 0.8% when combined with metformin and sulfonylurea. Byetta® was also studied in 233 patients uncontrolled on pioglitazone alone; decrease in A1C at 16 weeks was 0.8%.

Sitagliptin (Januvia®)

Sitagliptin (Januvia®) is the first in another new class of medications. Sitagliptin acts as an inhibitor of the enzyme dipeptidyl peptidase IV (DPP-4). This is the enzyme responsible for the degradation of GIP and GLP-1. By inhibiting the DPP-4 enzyme, the half life of endogenous GLP-1 is increased. Sitagliptin is approved as monotherapy or combination therapy with TZDs or metformin for the treatment of type 2 diabetes. Dosing for sitagliptin is simple; most patients receive 100 mg QD. However, for patients with renal insufficiency (CrCl between 30-50 mL/min) 50 mg QD is the maximum dose, and for patients with severe renal insufficiency (CrCl <30 mL/min) 25 mg QD is the maximum dose.

Unlike exenatide, this class of medication is available in an oral formulation and is generally weight neutral when used as monotherapy.

Adverse reactions seen in trials are mild and limited primarily to nasopharyngitis, upper respiratory tract infections, and headache. No major drug interactions have been identified.

To receive the monotherapy indication, sitagliptin was compared to placebo in an 18 week study enrolling 521 patients. A1C decreases of 0.6% and 0.48% respectively were detected. The authors concluded that sitagliptin was effective at improving glycemic control and was well tolerated in patients with type 2 diabetes who had inadequate glycemic control on diet and exercise alone.

Sitagliptin has also been used as an adjunct therapy in patients uncontrolled on pioglitazone alone. Sitagliptin plus pioglitazone resulted in an A1C decrease of 0.7% in a 24 week study enrolling 353 patients. Sitagliptin was not associated with more incidences of hypoglycemia than placebo.

Sitagliptin plus Metformin (Janumet®)

A combination product of sitagliptin and metformin (Janumet®) was approved in April 2007. It is indicated for patients that are not controlled on metformin or sitagliptin alone or for patients already taking metformin and sitagliptin as separate products. Janumet® is dosed BID, and is available as 50 mg sitagliptin + 500 mg metformin or 50 mg sitagliptin + 1000 mg metformin. Janumet® has the same contraindications and precautions as each of its components.

In a noninferiority trial, 1172 patients with type 2 diabetes not controlled on metformin alone were assigned to additional treatment with sitagliptin 100 mg QD or glipizide. Patients were followed for 52 weeks. A1C was decreased by 0.67% in both the sitagliptin and glipizide group, thereby confirming noninferiority. In this trial, body weight significantly decreased with sitagliptin by 1.5 kg and significantly increased with glipizide by 1.1 kg after 52 weeks.

Incretins Place in Therapy

Currently incretin therapy is not indicated as first line for patients with type 2 diabetes. Neither Byetta® nor Januvia® is mentioned in the ADA's treatment guideline for the management of type 2 diabetes. Metformin is still first line therapy, followed by insulin, sulfonylureas, or TZDs. The incretin class should be looked at as adjunct therapy. A1C decreases are not as significant with Byetta and Januvia as with other classes of antidiabetic agents. Also, Byetta® is associated with extensive nausea upon initiation of therapy, but patients typically develop tolerance as therapy continues. Byetta® is also only available as a BID injection.

Despite only modest decreases in A1C, Januvia® is generally well tolerated and available orally. Byetta® is typically associated with significant weight loss, while Januvia® is weight neutral or has small effects on weight loss. Weight gain is a significant issue with most of the other classes of antidiabetic agents. In patients with type 2 diabetes, any medication that could assist with weight loss or at least not cause weight gain should be looked on favorably. Since the incretin system is glucose dependent, this class of medications is not typically associated with less hypoglycemia. This could be beneficial for patients with hypoglycemic unawareness. The pros and cons of incretin therapy should be carefully weighed for each patient, but the incretin system represents a novel adjunct therapy for patients with uncontrolled type 2 diabetes.

References available upon request.