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An Update on Exenatide and Liraglutide for Type II Diabetes Mellitus

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Intro

Incretin hormones, such as gastric inhibitory peptide and glucagon-like peptide-1 (GLP-1), are produced in the intestines, and their combined effects are known as the incretin effect.[1] Glucagon-like peptide 1 (GLP-1) stimulates glucose-dependent insulin secretion, inhibits postprandial glucagon secretion, and slows gastric emptying, thus reducing appetite. Endogenous GLP-1 is degraded rapidly by the enzyme dipeptidyl peptidase-4 (DPP-4), resulting in an extremely short half-life. Newer treatments, such as exenatide, liraglutide and exenatide long-acting release (LAR), have been developed as medications that exert GLP-1 activity and yet resist DPP-4 inactivation. Exenatide was approved by the FDA in 2005 as an adjunct therapy for type 2 diabetes mellitus (T2DM). It was the first incretin mimetic to demonstrate a decrease in hemoglobin A_1C (HbA_{1c}) via glycemic control (average 1 percent reduction) and a significant decrease in body weight (1.6 – 5.3 kg reduction).[2,3] Liraglutide is the newest GLP-1 mimetic to be approved for T2DM, gaining approval in early 2010.[1] Unlike exenatide, which needs to be dosed twice daily, liraglutide is designed for once-daily dosing. A long-acting exenatide product, Bydureon® (exenatide LAR), is currently being developed for once-weekly dosing. With the recent approval of liraglutide and the possable approval of exenatide LAR, practitioners may find it valuable to assess how each GLP-1 agent will fit into therapy for T2DM.

Exenatide

The use of exenatide has widely been compared to the use of long-acting insulin for T2DM that is uncontrolled after initial therapies. Although long-acting insulin may offer a greater decrease in HbA_{1c} than exenatide, it causes weight gain, an unwanted effect in T2DM patients.[4] Over the past five years, exenatide has established a role within T2DM therapy, but long-term adverse events have also been noted with therapy.

Like other new treatments for T2DM, the adverse drug reaction (ADR) profile of exenatide has been a cause for concern as long-term treatment data becomes available. The most common ADRs associated with exenatide treatment are nausea, vomiting, diarrhea and hypoglycemia.[5] However, most of these ADRs occur in combination therapy with other T2DM medications and can be controlled through monitoring therapy.[5] In addition to minor adverse reactions with exenatide, as of Jan. 1, 2010, the FDA has received 36 post-marketing reports of acute pancreatitis, including six cases of hemorrhagic or necrotizing pancreatitis and two deaths.[2] However, it is important to note that 90 percent of these patients had confounding factors for pancreatitis (obesity, hyperlipidemia, hypertriglyceridemia, alcohol use).

Thirty additional cases were subsequently reviewed by the FDA, none of which resulted in fatality. Initial symptoms began at an average of 34 days after starting exenatide treatment, and abdominal pain was the most common symptom, occurring in 23 of the 30 patients. Symptoms subsided for 22 of the 23 patients after exenatide was discontinued; however, re-exposure caused a recurrence of symptoms in most patients.

Because of the controversy regarding the issue of pancreatitis with the use of exenatide, the manufacturer has recently made an addition to the package insert pertaining to patient monitoring.[6] The warning recognizes that patients should be monitored for symptoms of pancreatitis when treatment is started on the medication or if the dose is increased. If symptoms are consistent for diagnosis of pancreatitis, treatment should be discontinued immediately and the patient should be appropriately managed. These patients are then ineligible for any future treatment with exenatide.

The FDA also has received 78 cases of altered renal function in patients receiving exenatide treatment (62 acute, 16 renal insufficiency).[7] Initial symptoms occurred three days to two years after initiation of exenatide treatment in patients who were 23-83 years old. Fourteen of these patients had a past medical history of chronic kidney disease, a contraindication for exenatide treatment, and 95 percent had at least one risk factor for altered kidney function, such as cardiac insufficiency, hypertension, pancreatitis, rhabdomyolysis or urinary tract infection. Several patients were also at increased risk due to the use of antiretrovirals, antihypertensives, diuretics or NSAIDs. Four deaths were reported, and 91 percent of the treated patients required hospitalization. Symptoms improved in half of the patients after discontinuation of exenatide, while 18 patients required dialysis and two required a renal transplant. A precautionary statement has since been added to the labeling for exenatide about treatment in patients with low creatinine clearance (<50 mL/min).[5] Practitioners should continue to evaluate renal function prior to exenatide treatment and throughout the progression of T2DM in individual patients.

In late 2009, the FDA granted approval to use exenatide monotherapy in T2DM patients. The indication was granted after a study showed improved glucose control and weight loss in a 24-week, randomized, double-blind, placebo-controlled trial with 203 patients completing the study.[8] Patients were randomized to 5 mcg twice-daily or 10 mcg twice-daily dosing, with the primary endpoint of decreased HbA_{1c} and secondary endpoints of fasting serum glucose, postprandial glucose and weight. Results from the study showed a statistically significant decrease in mean postprandial glucose (5 mcg -17.5 mg/dL; 10 mcg -18.7 mg/dL; placebo -5.2 mg/dL; $p < 0.001$). Adverse events were similar between monotherapy and adjunct therapy, with nausea being the most common. The effectiveness of monotherapy compared to adjunct therapy has not yet been studied.

Exenatide Long-acting Release (LAR)

Amylin Pharmaceuticals, Eli Lilly, and Alkermes have developed a long-acting exenatide product, Bydureon® (exenatide LAR), which is a once-weekly form of Byetta. Recently, the FDA denied approval due to clarifications needed on labeling, risk evaluation and mitigation strategy (REMS), and the manufacturing process. At the time this article was written, Bydureon was still not FDA-approved, but the following two studies demonstrate its potential in the treatment of T2DM.

A 30-week, randomized, non-inferiority, comparator-controlled, open-label trial was performed comparing exenatide LAR 2 mg once-weekly to 10 mcg exenatide twice-daily to assess safety, efficacy, tolerability and non-inferiority of the long-acting product. This product was considered to be non-inferior if HbA_{1c} change was <0.4 percent at week 30. A total of 295 weight-stable patients with T2DM were included in this study. Subjects were either naïve to anti-diabetic treatment or were receiving one or more anti-diabetic agents, including metformin, sulfonylureas, thiazolidinediones or a combination, for at least two months prior to the trial. Patients were randomized into two groups, both receiving 5 mcg exenatide twice daily for three days, then either 2 mg exenatide LAR for 30 weeks or 5 mcg exenatide twice daily for 28 days followed by 10 mcg exenatide for the remainder of the 30-week study. Results showed that, by week 10, the once-weekly group had a significant decrease in HbA_{1c}, 1.9, compared to the twice-daily group, 1.5 (p=0.0023) despite patient background. The once-weekly group also had 77 percent of patients achieve HbA_{1c} of ≤7 percent compared to 61 percent in the twice-daily group (p=0.0039). The twice-daily group had 35 percent of patients with a baseline HbA_{1c} of ≥9 percent achieve a final HbA1c of ≤7 percent, while the once-weekly group had 65 percent of patients achieve this level (p=0.02). Bodyweight decreased in both the exenatide and exenatide LAR groups (-3.6 kg and -3.7 kg, respectively, p=0.89). Fasting plasma glucose levels significantly decreased in the once-weekly group versus the twice-daily group (-41.4 mg/dL and -25.2 mg/dL), respectively, p<0.0001). In addition, the Diabetes Treatment Satisfaction Questionnaire (DTSQ) showed a significant increase in satisfaction in the once-weekly group. Adverse events for the once-weekly group were mild and included nausea (26.4 percent) and injection site pruritus (17.6 percent) and were significantly lower than the twice-daily group. No major hypoglycemic events, occurrences of pancreatitis or significant abnormalities were found. Overall, both exenatide and exenatide LAR decreased HbA_{1c}. Significant reduction in HbA_{1c} values due to continuous exposure to exenatide indicate that glycemic control provided by the once-weekly formulation is not inferior to the twice-daily formulation.[12]

A 52-week, randomized, multi-center, open-labeled trial was performed to evaluate the effects of exenatide twice daily and exenatide once weekly on treatment satisfaction and quality of life. Patient-reported outcome instruments included DTSQ and the Impact of Weight on Quality Of Life (IWQOL-Lite), which were given at baseline and weeks 30 and 52. A total of 295 patients were included – 148 in the 2 mg exenatide once-weekly and 147 in the 10 mcg twice-daily during weeks 1-30, then 2 mg weekly for weeks 30-52. Results of the DTSQ scores showed that at week 52, treatment satisfaction improved in the once-weekly group. However, the IWQOL-Lite showed a significant increase in satisfaction in both groups (p<0.001), but there was no difference between them. After the twice-daily group switched to once-weekly exenatide, improvement was seen for treatment satisfaction, convenience, flexibility and continuance. In this group, the IWQOL-Lite also showed significant improvement in physical function and public distress. Overall, the weekly group had improved satisfaction with treatment convenience, flexibility and public distress. All comparisons were shown to be statistically significant with p<0.05. In addition, there was no difference in adverse events between the groups. Overall, the once-weekly form had improvement in satisfaction, convenience and flexibility. This could be a result of ease of use, less frequent administration, and greater improvement in glucose control with perceived hyperglycemia. The willingness to continue treatment could possibly improve adherence and, thus, the outcome and control of T2DM.[13]

Liraglutide

Recently approved by the FDA, liraglutide is authorized for use in T2DM as monotherapy or in combination with other anti-diabetic medications, such as metformin, thiazolidinediones or sulfonylureas.[1] The approval was delayed due to possible risk of medullary thyroid cancer, though malignant tumors were only evident in animal trials. Novo Nordisk, the manufacturer of liraglutide, funded the Liraglutide Effect and Action in Diabetes (LEAD 1-6) studies to establish the safety and efficacy of liraglutide. LEAD trials 1, 2, 4 and 5 primarily focused on combination therapy with liraglutide and one or more oral antidiabetic medication, whereas LEAD-3 focused on monotherapy, and LEAD-6 compared liraglutide with exenatide.

The LEAD-3 trial is a double-blinded, randomized trial performed to evaluate and compare the efficacy of liraglutide 1.2 mg and 1.8 mg once daily with oral glimepiride 8 mg once daily as monotherapy for T2DM.[9] A total of 746 participants with early T2DM were enrolled for the 52-week trial. Participants were 18-80 years old, had an HbA_{1c} between 7-11 percent, had a BMI of ≤40 kg/m², and had not used insulin or corticosteroids in the previous three months. Participants were placed into one of three treatment groups: 1.2 mg liraglutide (n=251), 1.8 mg liraglutide (n=247), or 8 mg glimepiride (n=248). At the completion of the trial, HbA_{1c} was reduced more significantly in both liraglutide therapies than glimepiride (Table 1). Greater decreases in HbA_{1c} were seen in patients previously treated with lifestyle modifications only as compared to those patients who had received oral anti-diabetic medications preceding the trial. Significantly more patients achieved the American Diabetes Association HbA_{1c} target of less than 7 percent in the liraglutide therapies as compared to glimepiride (table 1). No major hypoglycemia occurred, though minor hypoglycemia occurred in all three groups. Nausea was more prevalent in liraglutide groups but decreased after four weeks. The LEAD-3 trial was extended another 52 weeks with 440 patients entering the extra year of treatment.[10] After the extension period was completed, mean reductions in HbA_{1c} and those reaching the target goal were significantly greater with liraglutide 1.2 mg and 1.8 mg than glimepiride (table 1). Treatment with liraglutide is shown to be effective and safe as monotherapy and produces significant greater reductions in HbA_{1c} and FPG as compared with glimepiride.

The LEAD-6 trial is a 26-week randomized trial that compares the safety and efficacy of liraglutide with exenatide in T2DM patients not adequately controlled on metformin alone (n=127), a sulfonylurea alone (n=45), or metformin plus a sulfonylurea (n=292).[11] The 464 participants were 18-80 years old, HbA_{1c} between 7-11 percent, had a BMI of ≤45 kg/m², and had no previous insulin or exenatide. The patients continued on their treatment and were randomly chosen to receive either 1.8 mg liraglutide once daily (n=233) or 10 mcg exenatide twice daily (n=231). After 26 weeks, more patients reached target HbA_{1c} levels of <7 percent and had significantly improved glycemic control with liraglutide than exenatide (table 1). Both liraglutide and exenatide groups had similar weight reductions (table 1). The incidence of nausea was initially similar in both groups but was less persistent in the liraglutide group (p<0.0001). Treatment satisfaction was measured using the Diabetes Treatment Satisfaction Questionnaire. Overall, treatment satisfaction was significantly better with liraglutide (n=161) than with exenatide (n=143) (p=0.0004).

Table 1. Efficacy of liraglutide (LIRA) as monotherapy in the treatment of T2DM. Results from two LEAD trials. LEAD-3 compared LIRA against glimepiride (GLIM) for efficacy as monotherapy. LEAD-6 compared the efficacy of LIRA to exenatide (EXEN).[9, 10, 11]

Study	Therapy	No. of pts	Mean HbA1c (%)		Mean FPG (mg/dL)		Pts at ADA target HbA1c (%)	Body Wt (kg)	
			Baseline	Change	Baseline	Change		Baseline	Change
LEAD-3 (Mono)	LIRA 1.2mg	251	8.3	-0.84	167.4	-15.1	43	92.5	-1.85
	LIRA 1.8mg	247	8.3	-1.14	171	-26.8	51	92.8	-2.26
	GLIM 8mg	248	8.4	-0.51	171	-5.2	28	93.4	+1.22
LEAD-3 (Mono extension)	LIRA 1.2mg	149	8.1	-1.1	--*	-23.4	53	--	-2.1
	LIRA 1.8mg	154	8.1	-1.4	--	-27	58	--	-2.7
	GLIM 8mg	137	8.0	-0.6	--	-5.4	37	--	+1.1
LEAD-6 (Vs. EXEN)	LIRA 1.8mg	233	8.2	-1.12	176.4	-29	54	93.1	-3.24
	EXEN 10mcg	231	8.1	-0.79	171	-10.8	43	93	-2.87

*Baseline data not provided

Conclusion

New incretin based therapies have the possibility to influence the treatment of T2DM. Exenatide, liraglutide and exenatide LAR appear to be relevant to the treatment of T2DM in their ability to decrease HbA_{1c} while reducing weight and may be appropriate as monotherapy agents for some patients. Studies show that each agent exhibits a mild safety profile with modest differences in therapeutic outcomes. Currently, patient preference and dosing schedule should be considered by the practitioner when determining the preferred agent for the patient. Additional head-to-head trials may be beneficial to adequately compare exenatide, liraglutide, or exenatide LAR to further determine the specific role in therapy for each agent.

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