

Liraglutide: 52 Weeks and 59 lb Later

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PRESENTATION

V.T., a 48-year-old, morbidly obese, Caucasian woman who has had type 2 diabetes for 8 years presented to the diabetes clinic on 24 November 2010. During the previous year, her A1C values were 5.6% on 6 November 2009, 6.6% on 27 April 2010, and 5.8% on 28 October 2010. Through word of mouth, she had heard about a new medication, liraglutide, and inquired about its use for her diabetes.

She had tried to lose weight in the past by watching calories but had minimal success. She stated that she has always been overweight and weighed 217 lb when she first presented to our clinic on 4 February 2005. Her weight has been near 250 lb for 2 years. She asked whether she might substitute liraglutide for some of her present diabetes medications and said she wanted to use a medication that would help her lose weight instead of facing the continued weight gain she was experiencing.

She denied any hypoglycemia, polyuria, polydipsia, or polyphagia. Her medical history included morbid obesity, type 2 diabetes of 8 years' duration, gestational diabetes, hypertension, dyslipidemia, migraine headaches, iron deficiency, vitamin B₁₂ deficiency anemia, peptic ulcer disease, and sulfa allergy.

Her medications included:

- Metformin, 1,000 mg twice daily
- Glimepiride, 4 mg in the morning
- Pioglitazone, 45 mg daily
- Simvastatin, 40 mg before bed
- Lisinopril/hydrochlorothiazide, 20/25 mg daily
- Aspirin, 81 mg daily
- Fish oil, 2,000 mg daily
- Ferrous sulfate, 325 mg daily
- Cyanocobalamin IM, 1 mg every 3 months
- Sumatriptan, 50 mg as needed for migraine headache

V.T.'s physical exam was unremarkable. Her weight was 254 lb, height was 64 inches, and BMI was 43 kg/m². Her laboratory test values are shown in Table 1.

QUESTIONS

1. Will initiating liraglutide and stopping pioglitazone and glimepiride allow V.T. to lose weight while controlling her blood glucose and A1C?
2. Will her A1C continue to be < 7%?
3. Will discontinuing pioglitazone and glimepiride and beginning liraglutide improve the safety profile of her pharmacotherapy regimen by eliminating medication-related adverse events?
4. With an A1C of 5.8%, was she having hypoglycemia, and will modifying her pharmacotherapy regimen prevent hypoglycemia?
5. What support will she need to benefit from the liraglutide-induced satiety and lose weight

Table 1. V.T.'s Physical and Laboratory Test Results

Visit Date	28 October 2010	7 January 2011	9 May 2011	24 August 2011	30 November 2011
A1C (%)	5.8	6.0	6.2	6.7	5.4
Weight (lb)	254	238	216	206	195
BMI (kg/m ²)	43	41	37	35	34
Blood pressure (mmHg)	122/80	108/72	132/80	128/78	102/66
Total cholesterol (mg/dl)	131	101	115	128	141
LDL cholesterol (mg/dl)	57	38	48	76	80
HDL cholesterol (mg/dl)	55	36	43	37	38
Triglycerides (mg/dl)	97	136	119	74	117

(i.e., dietitian, diabetes support group, and physical activity)?

COMMENTARY

Liraglutide was approved for the treatment of type 2 diabetes by the U.S. Food and Drug Administration in January 2010. It is not approved for weight loss, but this is a common additional benefit of liraglutide and other drugs in the glucagon-like peptide-1 (GLP-1) receptor agonist class.

GLP-1 stimulates glucose-dependent insulin secretion and glucagon suppression, delays gastric emptying, increases satiety, and increases β -cell mass in rodents.¹ Because it is glucose dependent, it works when blood glucose is elevated but not when it returns to normal; hence, it has a low rate of hypoglycemia.

In 2009, an algorithm for glycemic control was published by the American Association of Clinical Endocrinologists and the American College of Endocrinology consensus panel on type 2 diabetes.² This algorithm stressed the importance of choosing therapies that have a low risk of hypoglycemia and weight gain.² Before the GLP-1 receptor agonists came to market, little could be done to control blood glucose without causing weight gain (except for metformin therapy).

Initial therapy for type 2 diabetes includes lifestyle modifications and metformin. Lifestyle therapy is aimed at reducing caloric intake and increasing physical activity to allow patients to lose weight and decrease insulin resistance. Metformin is a good first-line option because it usually causes modest weight loss and minimal hypoglycemia. Unfortunately, many other therapies for type 2 diabetes cause weight gain. In clinical practice, we have seen that weight gain is discouraging to patients and may lead to decreased adherence with medications and lifestyle modification.

V.T. had been on a combination of metformin, sulfonylurea, and rosiglitazone or pioglitazone since 2005. During that time, her weight had increased from 217 to 254 lb. Although her blood glucose was controlled on her current regimen of metformin, pioglitazone, and glimepiride, she did not want to continue gaining weight and wanted a medication that could help her lose weight. Besides excessive weight gain, V.T. was not experiencing hypoglycemia or any other side effects from her therapy regimen.

Achieving an A1C at goal is the primary treatment objective in diabetes, but when side effects of medications affect patients' quality of life, changes are warranted. The potential benefits to V.T. of stopping glimepiride and pioglitazone and starting liraglutide would be maintaining her A1C at $< 7\%$ and having an opportunity to lose weight through increased satiety. She continued on metformin, 1,000 mg twice daily, and liraglutide was started at 0.6 mg every night for 7 days, titrated to 1.2 mg every night for 7 days, and then to 1.8 mg every night thereafter.

Table 1 shows how this treatment modification affected V.T.'s weight. The addition of liraglutide resulted in considerable weight loss, from 254 to 195 lb (a 59-lb loss) over 52 weeks, and a BMI reduction from 43 to 34 kg/m². V.T. attributed the weight loss to a greater sense of satiety, resulting in decreased food intake. She did not initiate any diet or exercise program.

V.T. only experienced nausea from the liraglutide, a common but transient side effect, for the first 2 days of therapy. She was motivated by the ongoing positive outcome of her weight loss each week and continued to modify her food intake to continue losing weight over time.

V.T.'s A1C was 5.8% before starting liraglutide. The goal was to provide the same A1C lowering (to

$< 7\%$), while preventing hypoglycemia and weight gain and offering an opportunity to lose weight.

We also know that many therapies do not have the durability to control patients' blood glucose over time. In choosing a medication for type 2 diabetes, an important characteristic is the durability of its effect.

In ADOPT (A Diabetes Outcome Progression Trial),³ which studied the glycemic durability of rosiglitazone, metformin, and glyburide monotherapy, glyburide had a 5-year failure rate of 34%. In the Liraglutide Versus Glimepiride Monotherapy for Type 2 Diabetes (LEAD-3 mono) 52-week trial,⁴ liraglutide, 1.8 mg, showed a superior A1C reduction compared to glimepiride, 8 mg (1.14 vs. 0.51% (95% CI -0.83 to -0.42 , $P < 0.0001$). A1C values did not significantly increase with liraglutide, 1.8 mg, from week 12 to week 52 ($P = 0.33$), but they did significantly increase for glimepiride ($P = 0.0006$). In the 52-week extension of the LEAD-3 mono trial,⁵ patients completing 2 years of therapy showed an A1C reduction of 0.6% with glimepiride and 1.1% with liraglutide, 1.8 mg. The A1C reductions at 2 years were similar to those obtained at 1 year, thus showing sustained benefits in A1C reduction.

Part of the reason liraglutide may have a greater durability effect is that it may cause an increase in β -cell mass. If the pancreas is able to maintain or regenerate β -cell function, GLP-1 receptor agonists would be ideal for both initial and long-term therapy to attack one of the core defects in the disease progression of type 2 diabetes. V.T.'s A1C was maintained at $< 7\%$ during her first year of therapy, and her most recent A1C was 5.4%.

When modifying V.T.'s therapy, we questioned whether discontinuing

pioglitazone and glimepiride and initiating liraglutide would improve the safety profile of her pharmacotherapy regimen. V.T. did not experience any episodes of hypoglycemia with her previous drug regimen or during the past year after switching to metformin and liraglutide. We discontinued glimepiride because of the associated risk of hypoglycemia and weight gain.

In May 2011, V.T. started taking 0.5 mg glimepiride because her fasting blood glucose was in the range of 160–170 mg/dl. This did not result in any episodes of hypoglycemia. Because her A1C was 5.4% in November 2011 and she no longer had fasting hyperglycemia, we discontinued glimepiride again at that point.

The combination of glimepiride and pioglitazone can lead to a modest weight increase. In various clinical trials ranging from 16 to 24 weeks, patients on pioglitazone and a sulfonylurea had a median weight gain of 4.1 kg.⁶ Although V.T. did not have any edema or heart failure symptoms, pioglitazone can cause dose-dependent edema and a risk of developing heart failure.⁶ Another reason we discontinued pioglitazone was its association with a potential increased risk of fractures, especially in females.⁷

V.T. did experience nausea and had two episodes of vomiting during the first 2 days of therapy with liraglutide, 0.6 mg. After the first 2 days, she did not have any nausea or vomiting. Of concern, however, her HDL cholesterol decreased from a high of 55 mg/dl at baseline to a value of 38 mg/dl at her most recent visit. Discontinuation of pioglitazone may have been responsible for this reduction because pioglitazone at the 45-mg dose has been shown to increase HDL cholesterol from baseline by 19.1%.⁶ Because her

HDL cholesterol was below goal, we increased her over-the-counter fish oil supplement to 3,000 mg daily.

Comparing the minimal side effects experienced with liraglutide and the potential for adverse events with glimepiride and pioglitazone, we concluded that we had indeed improved the safety profile of her pharmacotherapy regimen. Liraglutide is an injectable agent, but this was not a barrier to V.T. because the potential benefit of weight loss outweighed any concern she had about injections.

CLINICAL PEARLS

- Nausea is a common side effect of liraglutide. Having patients take it in the evening may reduce any nausea because the peak concentration of the drug will occur while patients are sleeping.
- Patients are instructed to pay attention to their new sense of fullness and to stop eating as soon as they feel full. This decreases the incidence of nausea and leads to decreased food consumption. Because of the impact liraglutide had on V.T.'s appetite, other interventions were not necessary beyond discussing weight loss progress with a diabetes educator.
- Using diabetes medications that may cause weight loss, instead of weight gain, can have a motivating effect that may result in a larger weight reduction than those observed in clinical trials.
- Metformin and liraglutide in combination decreases the likelihood of hypoglycemia while allowing patients to maintain an A1C of < 7%.
- Patients should be educated about the risks and benefits of all medications available to treat diabetes. Clinical inertia should not prevent patients with diabetes from getting the best medication available to

allow them to achieve their goals safely.

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Note of disclosure: Dr. Peters has received honoraria for serving as a speaker and advisory board member for Novo Nordisk, which manufactures liraglutide.