Liraglutide and insulin:

concomitant administration of a GLP-1 agonist with insulin and effects on A1c, insulin dose, weight, fasting blood sugar, and blood pressure.

J. Robin Conway M.D., Andrea Lasso, DDS, Emily Hall BSc
Canadian Centre for Research on Diabetes, Smiths Falls, ON - Oct 10 2011

ABSTRACT

Liraglutide, a glucagon-like peptide-1 (GLP-1) agonist, has been shown to improve glycemic control in individuals with type 2 diabetes mellitus (T2DM) who fail to achieve blood glucose targets (A1c<7.0%) on metformin and sulfonylureas alone [1]. The concurrent use of liraglutide with insulin, however, has not been extensively reported[2,3,4]. In this year-long observational study we assess the efficacy of liraglutide in improving glycemic control in T2DM individuals who are already on insulin. Our observations on 85 patients suggest that the combination of liraglutide and insulin is safe and effective, with average A1c levels significantly decreasing over the observation period by 0.43% compared to baseline (p<0.05). Significant reductions in weight (-2.97kg) and total daily insulin dose (-22.29 units) were also observed. Further long-term studies assessing the concomitant use of liraglutide and insulin in T2DM patients are needed to determine if improvements in glycemic control are maintained over time.

PRIMARY OBJECTIVE: To assess whether adding liraglutide to standard therapy improves glucose control in obese, insulin resistant individuals with type 2 diabetes mellitus (T2DM) who fail to achieve glycemic targets (A1c<7.0%) despite treatment with insulin.

SECONDARY OBJECTIVE: To assess changes in weight, total daily insulin dose, fasting blood sugar, and blood pressure associated with liraglutide use in T2DM individuals already on insulin.

INTRODUCTION

One of the major challenges in treatment of type 2 diabetes mellitus (T2DM) is preserving glycemic control over time. Previous studies [5,6] have shown a progressive decrease in the number of T2DM patients achieving and maintaining glycosylated hemoglobin (A1c) targets (<7.0%) over extended periods of time. A particular difficulty has been treating the obese, insulin resistant T2DM patient who, despite large doses of insulin, fails to achieve glycemic targets. Furthermore, increasing weight in these patients has been a problem. Our reason for doing this study was to focus on the challenge of achieving glycemic control in the obese insulin resistant person with type 2 diabetes who requires insulin. There had been some anecdotal reports of improvement by introducing a GLP-1 agonist so we wanted to investigate this in a systematic manner.

In May 2010, the first of a new class of glucagon like peptide-1(GLP-1) agonists (Liraglutide, Novo Nordisk) became available in Canada for the treatment of T2DM. GLP-1 agonists bind to GLP-1 surface receptors on beta cells of the pancreas when glucose levels are high. Activation of these receptors increases levels of cyclic AMP, which stimulates endogenous insulin secretion from the pancreas until glucose levels have returned to normal physiological levels1. Studies have suggested that GLP-1 agonists may increase insulin sensitivity and enhance -cell responsiveness to glucose[7,8].

In this observational study, we investigate whether, in challenging patients already on insulin but not achieving A1c targets, the addition of the GLP-1 agonist liraglutide to their treatment program could result in improved glycemic control, as well as influence other parameters such as weight, total daily insulin dose, fasting blood glucose, and blood pressure.

MATERIALS AND METHODS

This observational study was carried out in a primary care practice setting on individuals who were prescribed liraglutide along with insulin. Patients gave informed consent to their data being included in this study and were notified prior to starting liraglutide that the use of a GLP-1 agonist in addition to insulin was not an approved therapy by Health Canada.

Inclusion criteria targeted overweight adult individuals (BMI>25) with a diagnosis of T2DM who were injecting at least one dose of insulin daily. Exclusion criteria were consistent with contraindications according to the liraglutide product monograph. These contraindications included patients with type 1 diabetes mellitus, patients with a personal history of medullary thyroid carcinoma or multiple endocrine neoplasm syndrome , patients who were pregnant or breastfeeding, and patients who were hypersensitive to liraglutide.

Data was collected on a total of 85 insulin-treated T2DM patients who were prescribed liraglutide between May 2010 and August 2011. Patients ranged in age from 44 to 88 years old, with the average patient age being 60 years of age. The average duration of diabetes for patients at study initiation was 17 years. Average A1c was 8.46% at baseline. Body mass index (BMI) ranged from 27 to 63, with the average BMI being 37.1. Average patient weight at baseline visit was 106.7 kg. Average fasting blood sugar (FBS) was 9.50 mmol/L. Average total daily insulin dose per patient was 103 units, or 0.97units/kg. Data was only collected on total daily insulin dose because most patients were taking basal insulin, we realized this as a shortcoming and future studies should describe basal and bolus insulin changes separately.

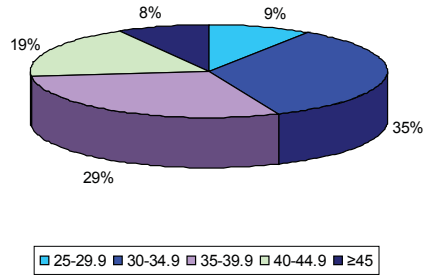


FIGURE 1. PATIENT BMI DISTRIBUTION AT BASELINE VISIT.

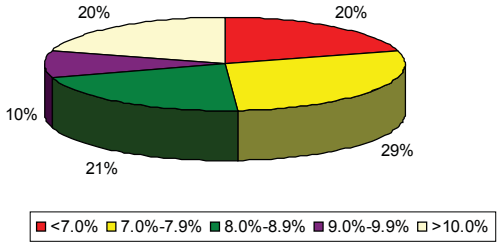


FIGURE 2. PATIENT A1C DISTRIBUTION AT BASELINE VISIT.

All patients were initiated at a dose of 0.6mg of liraglutide injected once daily, and then increased after one week to a dose of 1.2mg injected once daily. Depending on the response to 1.2mg, the dose was then increased to a maximum dose of 1.8mg of liraglutide daily if needed. Data for this study was collected over a 15 month time period. Mean changes in weight, A1c, FBS, total daily insulin dose, and blood pressure were observed from the time of liraglutide initiation (baseline visit) to 3 subsequent visits after baseline (follow-up visits 1, 2, and 3). On average, visits took place every 12 weeks. Observations at each visit were recorded and entered into a computer database. Data was analyzed at each follow up visit and compared to baseline values. Several two-tailed paired Student's t-tests were performed using Microsoft Excel 2007 to compare mean changes in A1c, weight, insulin dose, fasting blood sugar, and blood pressure at each visit.

RESULTS

HEMOGLOBIN A1C: Figure 3 reveals average hemoglobin A1c from baseline visit to follow-up visit 3 for patients on liraglutide and insulin. Average A1c was significantly reduced by 0.43% from baseline to follow-up visit 3 ($p<0.05$). Maximal A1c reduction was seen from baseline visit to follow-up visit 1. This follow-up visit generally took place 3-4 months after baseline. Average A1c dropped 0.56% at follow-up visit 1 compared to baseline, which was a statistically significant reduction ($p<0.05$). A modest increase in A1c can be seen at follow-up visits 2 and 3 compared to follow-up visit 1, suggesting that maximal A1c reduction

was not fully maintained over the one year observation period for individuals on liraglutide and insulin.

WEIGHT: Average patient weight from baseline visit to follow-up visit 3 for individuals on liraglutide and insulin is displayed in Figure 4. A continuous decrease in weight was observed across all visits, with the majority of this weight reduction (-1.97kg) occurring between baseline and follow-up visit 1. Average weight was significantly reduced from baseline visit to follow-up visit 3 by 2.97kg ($p<0.05$). In general, weight reduction appeared to be maintained over the observed treatment period of approximately one year.

INSULIN DOSE: Average total daily insulin dose from baseline visit to follow-up visit 3 can be seen in Figure 5. Overall, average daily insulin dose per patient was significantly reduced by 22.29 units by follow-up visit 3 compared to baseline values ($p<0.05$). Insulin requirement per kilogram of body weight fell from an average of 0.97units/kg at baseline to 0.77units/kg by follow-up 3. The largest insulin dose reduction (-21.03 units) was seen between baseline visit and follow-up visit 1. After follow-up visit 1, insulin dose decreased slightly over the final two follow-up visits.

AVERAGE FBS: Average FBS levels from baseline visit to follow-up visit 3 can be seen in Figure 5. Trends observed in FBS followed a similar pattern to average A1c levels; the largest decrease was seen from baseline visit to follow-up visit 1, with values slightly increasing at follow-up visits 2 ad 3. While the 1.21 mmol/L decrease in average FBS from baseline to follow-up 1 was significant ($p<0.05$), overall average FBS reduction of 0.60 mmol/L from baseline to follow-up 3 was not ($p>0.05$). These results suggest that glycemic control was not entirely preserved throughout the liraglutide treatment period.

BLOOD PRESSURE: Average systolic and diastolic blood pressure levels from baseline visit to follow-up visit 3 are displayed in figures 6 and 7, respectively. Observed change in blood pressure across all visits was not statistically significant ($p>0.05$).

ADVERSE EVENTS REPORTED BY PATIENTS ON LIRAGLUTIDE AND INSULIN

The following are adverse events experienced by patients on liraglutide and insulin, as well as various other reasons for discontinuation.

Hypoglycemia (1 or more glucose readings <3.5mmol/l since baseline visit): reported by 15 people (=17.6%); did not lead to anyone discontinuing the drug.

Nausea & other GI side effects: Experienced by 17 people (20%), of which 8 people discontinued the drug (=9.4% discontinuation rate due to nausea & other GI side effects).

Unable to afford liraglutide: resulted in 8 people discontinuing the drug (=9.4% discontinuation rate).

Lack of effect in reducing a1c or weight: 8 people discontinued (=9.4% discontinuation rate).
RASH: experienced by 1 person, did not result in discontinuation (1.12%)

Lower abdominal pain: experienced by 1 person, lead to discontinuation (1.12%)

Drug discontinued by another doctor: 1 person (1.12%)

Desired weight loss achieved: 1 person discontinued (1.12%)

Death: 1 person (1.12%). This was a 62 year old lady with a 25 year history of diabetes, treated with Analog Premix insulin 80u a day in divided doses and metformin 2000 mg a day. A1c at baseline visit was 11.8%. She was started on 1.2mg of liraglutide daily and was titrated to a dose of 1.8 mg a day. Her fasting glucose fell from 16 to 4.7 mmol/L and average glucose from 21.5 to 12.3 mmol/L. Two months after starting liraglutide, she was admitted to the hospital with a wound dehiscence from a previously infected surgical incision. She developed septic shock and 6 days later had a cardiac arrest. She was transferred to a tertiary care centre on a respirator but did not recover and died a month later. Death is not regarded as being related to liraglutide therapy.

Total number of people who discontinued: 28 (=overall discontinuation rate of 33%).

FIGURE 2. AVERAGE HEMOGLOBIN A1C FROM BASELINE VISIT TO FOLLOW-UP VISIT 3.

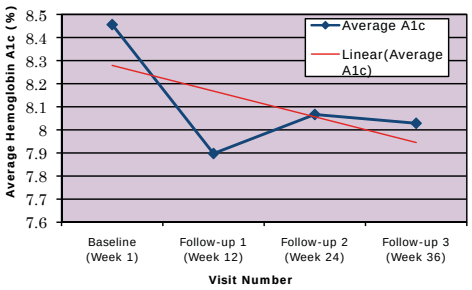


FIGURE 3. AVERAGE PATIENT WEIGHT FROM BASELINE VISIT TO FOLLOW-UP VISIT 3.

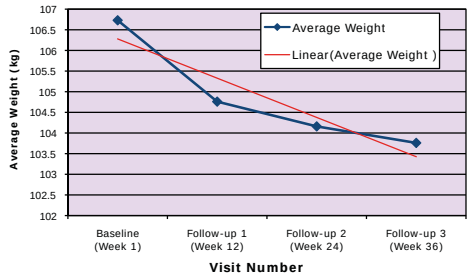


FIGURE 4. AVERAGE TOTAL DAILY INSULIN DOSE FROM BASELINE VISIT TO FOLLOW-UP VISIT 3.

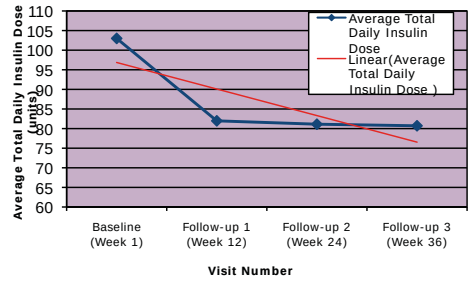


FIGURE 5. AVERAGE FASTING BLOOD SUGAR LEVELS FROM BASELINE VISIT TO FOLLOW-UP VISIT 3.

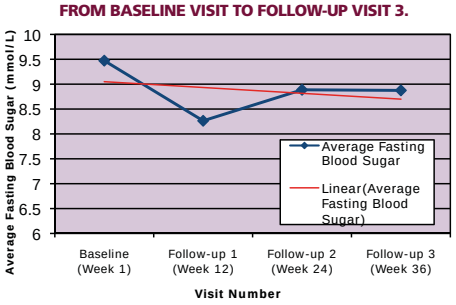


FIGURE 6. AVERAGE SYSTOLIC BLOOD PRESSURE FROM BASELINE VISIT TO FOLLOW-UP VISIT 3.

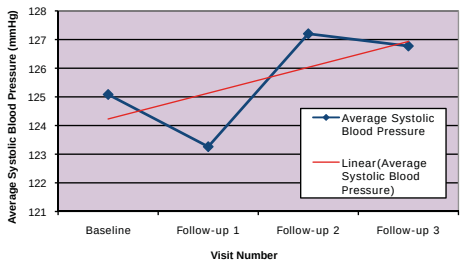
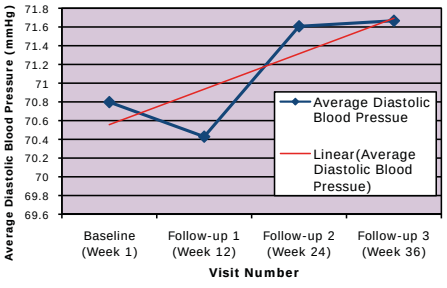


FIGURE 7. AVERAGE DIASTOLIC BLOOD PRESSURE FROMBASELINE VISIT TO FOLLOW-UP VISIT 3.



DISCUSSION

Addition of liraglutide to standard treatment in insulin-requiring T2DM patients over a one year period led to improvements in glycemic control, as demonstrated by average A1c reduction of 0.43%, average decrease in body weight of 2.97kg, and average decrease in total daily insulin dose of 22.29 units. Maximal improvements in glucose levels were generally seen in the 3 to 4 month period following baseline visit. The slight increase in average A1c levels from the first follow up visit to the second may have been the result of the large decrease in average daily insulin dose that was seen at follow-up visit 1 (an average reduction of 21 units per patient from baseline). Insulin requirements were reduced from an average of 0.97units/kg at baseline to 0.77units/kg at follow-up visit 1, suggesting that insulin sensitivity may have improved with liraglutide treatment. A decrease in average FBS was also seen, but this reduction was only found to be significant from baseline visit to follow-up visit 1 and was not maintained over the final two visits. No significant improvement in blood pressure was observed. The fact that the majority of patients (70%) had already achieved blood pressure targets of <130/80mmHg prior to liraglutide initiation may account for the minimal changes seen in blood pressure.

Changes in A1c, weight, FBS, insulin dose, and blood pressure were not predicted by BMI quintiles, however; it was observed that those with a BMI<30 at baseline generally showed no significant benefit from addition of Liraglutide to insulin therapy.

SHORTCOMINGS

This was a short observational proof of concept study in a single practice with a large number of people with diabetes. We had neither requested nor received financial or other assistance with this study. While we felt that this decreased potential bias, it also meant that subjects paid for their own medication, so numbers were small and many subjects had to discontinue the drug since they could not afford to purchase it. There is a non-blinded bias factor, the number of subjects is small and we reported insulin as total daily dose rather than looking separately at basal and bolus effects of the treatment. It is hoped that the positive results of this small pilot study will stimulate the design of a more comprehensive randomized control trial.

CONCLUSIONS

The combination of insulin and liraglutide in individuals with T2DM appeared to be safe and effective. Further randomized controlled studies are needed to investigate the benefit of liraglutide in improving and preserving glycemic control in insulin-requiring T2DM patients over time.

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