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ABSTRACT

OBJECTIVE: The objective of this systematic review is to determine whether or not liraglutide is safe and effective as a monotherapy for the treatment of obesity in type 2 diabetics and healthy individuals.

STUDY DESIGN: Review of three English language, primary, double-blind, randomized, controlled trial studies from 2004, 2007, and 2009

DATA SOURCES: Randomized, double blind, placebo-controlled trials comparing liraglutide to placebo, Orlistat, or Metformin were found using Ovid, MEDLINE, and COCHRANE databases

OUTCOMES MEASURED: Each of the three trials involved varying doses of liraglutide. The primary outcome measured in all three studies was reduction in bodyweight. Feinglos et al. monitored patient's weight on weeks -4, 0, 1, 4, 8, 12, and a follow-up visit. Astrup et al. recorded weight loss weekly for the first 4 weeks, and then every other week for the rest of the 20 week trial. Volsboll et al. weighed patients at baseline and then at the completion of the 14 week treatment. Adverse events were determined as those participants that experienced gastrointestinal upset and those that did not.

RESULTS: All three RCT's included in this review found that liraglutide helps with weight loss in both type 2 diabetics and nondiabetic obese individuals. While Astrup et al. and Vilsboll et al. proved the highest dosages of liraglutide were superior to Orlistat and placebo for weight loss, Feinglos et al. showed comparable results of weight reduction when comparing liraglutide to Metformin. In all three trials, the most common adverse events were gastrointestinal side effects, including nausea, vomiting, and diarrhea.

CONCLUSIONS: The results of the Astrup et al. and Vilsboll et al. show that use of liraglutide as a monotherapy for type 2 diabetics and nondiabetics is effective for treating obesity. These studies demonstrated that dosages above 1.90mg were most successful for weight reduction. However, dosages of liraglutide below 0.75mg, as was used in Feinglos' study, are not as effective.

KEY WORDS: Obesity, weight loss, liraglutide, type 2 diabetics

INTRODUCTION

Obesity is a substantial public-health crisis in the United States, and its prevalence is increasing in developing nations worldwide. Globally, at least 300 million people are clinically obese. In America, 60% of people are overweight and nearly 30% are obese. The annual cost of managing obesity in the US is ~$117 billion, of which, ~$52 billion are direct costs of healthcare and nearly $33 billion is spent annually on weight-loss products and services.[5]

Excessive caloric intake and inadequate caloric expenditure lead to obesity and predispose individuals to type 2 diabetes. Being overweight puts added pressure on the body's ability to properly control blood sugar using insulin and therefore makes it much more likely for a person to develop diabetes.[7] Additionally, obesity and type 2 DM are risk factors for cardiovascular disease, the leading cause of death worldwide and a major concern for Physician assistants working in any field.[4] Healthcare providers have been searching for new ways to decrease obesity rates, improve diabetic care, and subsequently improve quality of life for Americans.

There are few safe and effective drugs currently available for the treatment of obesity. Healthcare providers suggest Xenical (Orlistat), Phentermine (Apidex-P), or the over-the-counter diet pill Alli ® as a few options to facilitate weight loss in the overweight and obese. While these therapies may provide modest weight loss, researchers are looking for more safe and effective options for weight reduction.

Diabetics, unfortunately, face an added concern as tight glucose control, while important for preventing complications of the disease, often leads to weight gain. Metformin, a commonly

used therapeutic agent for diabetes, lowers blood glucose without inducing weight gain making it one of the more successful treatment options for type 2 diabetics.[2] However, Metformin is not effective for weight reduction.

Liraglutide, a drug initially used for glycemic control in type 2 diabetics, is a glucagon-like peptide-1 (GLP-1) analogue with structural similarity to the human GLP-1. GLP-1 is a gut-derived incretin hormone that suppresses appetite and delays gastric emptying. Obese individuals and type 2 diabetics have been shown to have an attenuated GLP-1 response to meals.[2] Researchers proposed that a once daily subcutaneous injection of liraglutide, in combination with a low-fat diet and physical activity, would cause weight reduction and glucose control offering an appealing option for both type 2 diabetes and obesity.

OBJECTIVE

The objective of this systematic review is to determine whether or not liraglutide is safe and effective as a monotherapy for the treatment of obesity in type 2 diabetics and healthy individuals.

METHODS

Criteria used for the selection of studies included obese patients $\geq$18yo with or without type 2 diabetes. The intervention assessed in these studies was varying doses of Liraglutide in comparison to Orlistat or placebo in non-diabetic patients, and Metformin or placebo in type 2 diabetics. Outcomes studied were dose-dependent reductions in body weight. Adverse reactions

such as severity of gastrointestinal discomfort, including nausea, vomiting, and diarrhea were also taken into account.

The search for articles was performed using OVID, MEDLINE, and Cochrane. Key words used in the search included “obesity”, “weight loss”, “type 2 diabetics”, and “liraglutide”. Articles were selected based on the importance of outcomes to the patient (Patient Oriented Evidence that Matters, or POEMS). The three studies chosen were randomized, double-blind control trials of liraglutide in comparison to Orlistat, Metformin, or placebo. All articles were published in English and all were published in peer-reviewed journals from 2004 to 2009. Inclusion criteria was based on studies that used liraglutide as a monotherapy, were randomized, controlled, and were based on patient oriented outcomes. Exclusion criteria involved studies that focused on combination treatment with liraglutide. Statistics reported included *p*-values, confidence intervals (CI), relative risk increase (RRI), absolute risk increase (ARI), and numbers needed to harm (NNH).

Table of demographics of included studies (Table 1)

Study	Type	# Pts	Age (yrs)	Inclusion Criteria	Exclusion Criteria	W/D	Interventions
Astrup, 2009 (1)	Randomized, double-blind, placebo-controlled 20-week trial	564	18-65	Aged 18-65 BMI 30-40kg/m^2 Stable bodywt. (<5% change in previous 3 months) -FPG < 7mmol/L	Type 1 or 2 diabetes Obesity induced by drug tx Use of wt-lowering pharmacotherapy or participation in a clinical wt. control study in past 3 mos. Previous surgical obesity tx Major medical conditions	74	-Liraglutide 1.2, 1.8, 2.4, or 3.0mg SQ QID
Feinglos, 2004 (2)	12 wk, randomized, multicentre, double-blind, parallel-group, double-dummy study	210	18-75	Aged 18-75 Type 2 diabetics (BMI 27-42 kg/m^2) who received at least 3 months of previous tx with an OAD monotherapy -HbA_{1c} $\leq$10%	High levels of anti-GAD ALT ($\geq$2x upper normal range) Serum Cr ($\geq$ 133mmol/L or 1.5mg/dL for males and $\geq$124mmol.l or 1.4mg/dL for females) Unstable cardiac dz, uncontrolled HTN, proliferative retinopathy, autonomic neuropathy, or recurrent severe hypoglycemia Use of drugs which could interfere with glucose levels or bodywt. C/I to metformin use, tx with thiazolidinediones, or chronic use of insulin (>7days) w/in past 3 mos	31	-Liraglutide 0.045, 0.225, 0.45, 0.5, and 0.75mg
Vilsboll, 2007 (3)	Double-blind, randomized, and placebo-controlled trial	165	$\geq$18	$\geq$18yo w/ type 2 diabetes and A_{1c} $\geq$7.5 and $\leq$10.0% FPG 7-13 mmol/L Previous therapy d/c	FPG > 15mmol/L during the study	25	Liraglutide 0.65, 1.25, or 1.90mg SQ QD

OUTCOMES MEASURED

The primary outcome measured in all three studies was reduction in bodyweight. In Feinglos et. al's 12 week trail they measured participants' bodyweight, taking an average of three consecutive morning fasting measurements, at each visit. This was done on weeks -4, 0, 1, 4, 8, 12 and a follow-up visit.[2] In Astrup et. al's study bodyweight was taken weekly for the first 4 weeks of the 20 week, and thereafter participants were assessed about once every 2 weeks. Standardized assessments of waist circumference were made on initial visit and every 4 weeks thereafter.[1] Vilsboll et. al conducted a study in which total bodyweight reduction after the 14 week trial was the measured outcome.[6]

All three studies also assessed adverse reactions, as liraglutide has been known to most notably affect the gastrointestinal tract. In each trial, the proportion of subjects with treatment emergent adverse events (TEAEs) was recorded for each treatment group.

RESULTS

The three randomized, controlled trials presented in this review involved data presented as an intention to treat analysis. All participants were randomly selected to receive treatment to reduce bodyweight. The Astrup et al study compared liraglutide to placebo and Orlistat in obese, non-diabetic patients over 12 weeks of treatment. Participants received 1.2, 1.8, 2.4, or 3.0mg of liraglutide once a day by subcutaneous injection; placebo once a day by subcutaneous injection; or Orlistat 120mg three times a day orally.[1] The other two studies focused on obese, type 2 diabetic patients. Feinglos et al compared five liraglutide doses, 0.045, 0.225, 0.45, 0.6, and

0.75mg taken subcutaneously once a day to Metformin 1000mg taken orally twice a day over a 12 week trail.[2] Visboll et al used liraglutide once daily subcutaneous injections at dosages of 0.65, 1.25, or 1.90mg compared to placebo once daily injections in their 14 week trial.[6] Inclusion criteria for all three studies were similar, as seen in **Table 1**.

In the Astrup study 564 participants were randomly assigned and 472 (84%) completed the trial. Three individuals treated with liraglutide (1.2, 2.4, and 3.0mg) were excluded due to missing post-baseline weight data. Major protocol deviations included non-compliance with eligibility criteria (n=3), assessments at week 20 outside visit window (n=12), treatment compliance issues (n=7), and trial drug dispensing errors (n=1); these people were excluded.[1] In Feinglos' trial 210 subjects were randomized, while 179 (85%) participants completed the study. This reduction due to withdrawal because of adverse events (n =7), ineffective therapy (n=9), non-compliance with protocols (n=5), and other reasons (n=10).[2] Lastly, Visboll's study included the least amount of randomized participants, numbering 165. Twenty-five were withdrawn due to adverse events (n=7), noncompliance (n=2), ineffective therapy (n=14), other (n=2).[6]

All three studies presented the primary outcome in continuous form that could not be converted to dichotomous data. They focused on mean reduction in body weight from baseline. In the Astrup study, those participants receiving the varying liraglutide dosage, all showed greater decreases in bodyweight after the 20week trial when compared to control groups. Mean changes in bodyweight were recorded as 6.7, 7.1, 7.9kg weight loss in the 1.2, 1.8, and 2.4mg dosage groups respectively. The largest average weight reduction was seen in 3.0mg dose group losing 9.1kg compared to the 4.1kg loss in those on placebo and 5.5kg loss in those participants

on Orlistat. Mean changes in bodyweight with liraglutide was significantly greater at all dosage levels when compared to placebo or Orlistat in obese non-diabetics.[1]

The Feinglos study compared percentage change in bodyweight throughout the trial. After 12 weeks, the metformin group had a slight weight loss of -0.61% (p= 0.124 relative to baseline), whereas the five liraglutide groups had a weight loss ranging from -0.05% (0.45mg, p=0.825 relative to baseline) to -1.87% (0.225mg, p=0.006 relative to baseline). The percentage of weight change in the five liraglutide dosage groups was not significantly different from the metformin therapy.[2]

In Volsboll's study bodyweight decreased in all treatment groups, 1.90mg, 1.25mg, 0.65mg, and placebo. Maximum estimated loss of 2.99kg was noted in the 1.90mg liraglutide group. The difference compared with placebo was significant only for the 1.90mg group (-1.21kg [95%CI -2.36 to -0.06] p=0.0390).[6]

In each of the studies participants experienced adverse gastrointestinal effects. This data was reported as the number of participants that experienced constipation, diarrhea, nausea or vomiting. This information was presented in dichotomous form as those that experienced GI adverse events and those in the study that did not. Through this comparison the "control event rate" (CER) was determine as those receiving placebo who experienced GI disorders and the "experimental event rate" (EER) as those administered liraglutide who had GI adverse events. Using these numbers the relative risk increase (RRI) and the absolute risk increase (ARI) were calculated. The numbers need to harm (NNH) was then computed to find out how many people

would have to be treated with liraglutide in order for one person to experience adverse events. The calculated analysis of outcomes and numbers needed to harm can be seen in **Table 2**.

Table 2. Analysis of Outcomes and NNH in Percentage of Patients Experiencing Adverse GI Effects with Liraglutide vs. Placebo

Study	# completed study	CER	EER	RRI	ARI	NNH
Astrup	564	30.6%	71.0%	1.32%	40.4%	2
Feinglos	179	8.8%	6.3%	-28%	-2.5%	-40
Vilsboll	140	23%	37%	61%	14%	7

DISCUSSION

The three studies addressed in this paper show, at higher dosages, liraglutide is effective in bodyweight reduction for obese individuals with and without type 2 diabetes. Additionally, the studies show other benefits for diabetics including tight glycemic control and lowering of HbA1c. However, concerning adverse events have been found that are not mentioned in any of the three studies. Black box warnings state that liraglutide has been associated with an increased risk of thyroid C-cell focal hyperplasia and C-cell tumor in rodent studies; however, it has unknown relevance in humans. Another safety concern is a possible increased risk of pancreatitis attributable to drugs that act through the GLP-1 pathway.[3] Considering this, the FDA granted approval of liraglutide on the basis of careful consideration of the drug's benefits, weighed against several complex safety-related concern.

The studies chosen for this review did have certain limitations, as the reduction of bodyweight was based on use of randomly selected therapy as well as proper diet and exercise. This may have affected outcomes as varying amounts of exercise and dietary control were

naturally present among participants. Also, concealing which therapy patients received may have caused blinding to be compromised. The trials were masked for liraglutide and placebo as both were given as once a day subcutaneous injections. However, the individuals in Astrup's and Feinglos' studies were given open label Orlistat and Metformin, respectively, thus introducing a potential for bias.[1]

CONCLUSION

The studies reviewed demonstrate that at higher dosages, liraglutide offers a safe and effective option for the treatment of obesity for individuals with and without type 2 diabetes. As proved by Astrup's 20 week study, administration of once daily liraglutide 2.4mg and 3.0mg subcutaneous leads to significant weight loss and in turn, reduction in rates of prediabetes.[1] Furthermore, in Vilsboll's study in spite of improved in glycemic control, which is usually associated with weight gain in type 2 diabetics, liraglutide offered a dose-dependent decrease in bodyweight.[6] While Feinglos' study showed treatment with liraglutide at doses of 0.045-0.75mg resulted in reductions in weight, these findings were comparable with the metformin control group.[2] This leads to the conclusion that levels of Liraglutide above 0.75mg will prove effective in weight reduction. Further testing starting at higher dosages should be performed.

Long-term effects of liraglutide on bodyweight need to be addressed. While liraglutide led to weight loss and improved several factors associated with cardiovascular events during these trials, the long-term risk-benefit and weight maintenance capabilities, still need to be established.[1]

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