Medicines Evidence Commentary

commentary on important new evidence from Medicines Awareness Weekly

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Obesity: liraglutide for weight loss among people with type 2 diabetes (SCALE study)

A double-blind randomised controlled trial found that in overweight or obese people with type 2 diabetes who were on a calorie controlled diet and exercise regimen, those taking liraglutide 3.0 mg daily lost statistically significantly more mean body weight (6.0%) than those taking placebo (2.0%) over 56 weeks. However the number of adverse events including gastrointestinal events and episodes of hypoglycaemia were statistically significantly higher with liraglutide 3.0 mg than with placebo and this led to more treatment withdrawals (9.2% compared with 3.3%). The 3.0 mg dose of liraglutide (Saxenda) that has been specifically developed for weight management is not available in the UK. It is important that prescribers do not confuse this new liraglutide product with the existing product (Victoza). Prescribers should continue to follow NICE guidance on the identification, assessment and management of obesity which recommends considering pharmacological treatment only after dietary, exercise and behavioural approaches.

Overview and current advice

Obesity is a factor in many serious illnesses including type 2 diabetes, heart disease and certain cancers. Adults with a body mass index (BMI) over 30 kg/m^2 are classified as obese and those with a BMI of 25 to 29.9 kg/m^2 are classified as overweight. According to NICE advice on preventing obesity and helping people to manage their weight, in England in 2011, 65% men, 59% women and around 30% of children aged 2-15 years were obese or overweight, with a predicted rising cost to the economy (including the NHS) of £50 billion a year by 2050. Obesity is a complex problem. Treatment of choice involves multicomponent interventions such as weight management programmes, behaviour change strategies, increasing people's physical activity levels or decreasing inactivity, improving eating behaviour and the quality of the person's diet, and reducing energy intake.

An individualised tailored approach to a planned weight management programme, taking into account the person's preferences, initial fitness, health status and lifestyle is recommended by NICE in the guidance on identification, assessment and management of obesity. NICE recommends
considering pharmacological treatment only after dietary, exercise and behavioural approaches have been started and evaluated and for people who have not reached their target weight loss or have reached a plateau on dietary, activity and behavioural changes. Orlistat is currently the only pharmacological treatment option recommended by NICE as part of a weight management plan in people who are obese or overweight with associated risk factors, such as type 2 diabetes and with the caveat of continuing orlistat therapy beyond 3 months only if the person has lost at least 5% of their initial body weight since starting drug treatment. Rates of weight loss may be slower in people with type 2 diabetes, so less strict goals than those for people without diabetes may be appropriate.

Liraglutide 6 mg/ml solution (Saxenda) is the first GLP-1 receptor agonist to receive a European marketing authorisation for weight loss, although at the time of publication it is not available in the UK. Saxenda is licensed as an adjunct to diet and exercise, to help manage weight in adults who are:

- overweight (have a BMI of 30 kg/m² or more) or;
- obese (have a BMI between 27 and 30 kg/m²) and have at least 1 weight-related complication such as dysglycaemia (pre-diabetes or type 2 diabetes), dyslipidaemia (abnormally high levels of cholesterol in the blood), hypertension or obstructive sleep apnoea (frequent interruption of breathing during sleep).

One pre-filled dial-a-dose Saxenda pen contains 18 mg liraglutide in 3 mL, delivering doses of 0.6 mg, 1.2 mg, 1.8 mg, 2.4 mg and 3.0 mg. The starting dose is 0.6 mg daily and should be gradually increased to 3.0 mg daily in increments of 0.6 mg with at least 1 week intervals. According to the summary of product characteristics for Saxenda, treatment should be discontinued after 12 weeks on the 3.0 mg daily dose if patients have not lost at least 5% of their initial body weight.

The only formulation of liraglutide 6 mg/ml solution (Victoza) available in the UK is indicated for the treatment of adults with type 2 diabetes to achieve glycaemic control in combination with oral glucose-lowering medicinal products and basal insulin or in combination with basal insulin alone, when these, together with diet and exercise, do not provide adequate glycaemic control. One pre-filled dial-a-dose Victoza pen contains 18 mg liraglutide in 3 mL, delivering doses of 0.6 mg, 1.2 mg and 1.8 mg. The starting dose is liraglutide 0.6 mg daily increasing after at least 1 week to 1.2 mg daily, up to a maximum of 1.8 mg daily based on clinical response. The NICE technology appraisal of liraglutide recommends liraglutide 1.2 mg daily as a possible treatment for some people with type 2 diabetes, but does not recommend the 1.8 mg daily dose because there was no robust evidence of additional benefits on glycaemic control from a higher dose, and a lack of clinical trials investigating dose escalation. Treatment should only be continued if there is a reduction in HbA1c of at least 11 mmol/mol (1.0%) and a weight loss of at least 3% of initial body weight at 6 months.

The NICE pathways on diabetes and obesity bring together all related NICE guidance and associated products on the conditions in a set of interactive topic-based diagrams.

New evidence

A multinational, randomised controlled trial (RCT)¹ investigated the efficacy and safety of liraglutide compared with placebo for weight management in adults who were overweight or obese and had type 2 diabetes. The 56-week double-blind placebo-controlled, parallel-group study was conducted in 126 sites in 9 countries (including the UK). A 12-week treatment-free follow-up period assessed treatment cessation effects.

Participants were adults (mean age 55 years, n=846) with a BMI of 27 kg/m² or more (mean 37.2 kg/m²), a stable body weight (less than 5 kg change in the last 3 months, mean 106 kg) and type 2 diabetes (HbA1c between 53 mmol/mol and 85.8 mmol/mol [7.0% and 10%]), mean duration of diabetes 7.2 years, treated with diet and exercise alone (around 12%) or in combination with 1 to 3 oral hypoglycaemic drugs (metformin, sulfonylurea, thiazolidinedione). More than half of participants were taking metformin alone and approximately a third were on a combination of oral hypoglycaemics.
Participants taking a sulfonylurea were asked to reduce their dose by 50% to mitigate the risk of hypoglycaemia. Allocation was concealed.

Participants were randomised in a 2:1:1 ratio to liraglutide 3.0 mg, liraglutide 1.8 mg (which is not indicated for weight management) or matched placebo for 56 weeks. Study drug was administered daily by subcutaneous injection using a modified insulin pen device. Participants were encouraged to follow a specified caloric controlled diet (500 calories per day deficit) and exercise programme (150 minutes or more per week of brisk walking).

The 3 co-primary outcomes were relative change in body weight, the proportion of participants losing 5% or more of their baseline body weight and the proportion of participants losing 10% or more of their baseline body weight, all measured at week 56. Secondary outcomes included changes in HbA1c, BMI, waist circumference, blood pressure, lipid profile and quality of life scores, although all were considered exploratory end points and the results are not discussed in this article. Analysis was conducted in the modified intention-to-treat (mITT) population (defined as all participants receiving at least 1 dose of study drug and with at least 1 post baseline efficacy assessment) and using the last observation carried forward (LOCF) to account for missing data. Safety data were evaluated on the safety analysis set (all exposed participants).

After 56 weeks, mean weight losses of 6.0% (6.4 kg), 4.7% (5.0 kg) and 2.0% (2.2 kg) from baseline were observed for liraglutide 3.0 mg, 1.8 mg and placebo respectively. Estimated treatment differences between liraglutide 3.0 mg and placebo and for liraglutide 1.8 mg and placebo were both statistically significant (4.00%, 95% confidence interval [CI] 5.10 to 2.90) and 2.71% [CI 4.00 to 1.42] respectively, p<0.001 for both comparisons). A statistically significantly higher proportion of participants lost 5% or more body weight (estimated treatment difference 32.9% [CI 24.6 to 41.2] and 19.0% [CI 9.1 to 28.8], p<0.001 for both comparisons) with liraglutide 3.0 mg and liraglutide 1.8 mg respectively compared with placebo. Similarly, a statistically significantly higher proportion of participants lost more than 10% body weight in the active treatment groups (estimated treatment difference liraglutide 3.0 mg: 18.5% [CI 12.7 to 24.4], p<0.001 and liraglutide 1.8 mg: 9.3% [CI 2.7 to 15.8], p<0.006) compared with placebo. More people treated with liraglutide (both strengths) than placebo reduced their net use of oral hypoglycaemics after 56 weeks.

Treatment-emergent adverse event rates were higher with liraglutide than with placebo (92.9%, 90.5% and 85.8% for liraglutide 3.0 mg, liraglutide 1.8 mg and placebo respectively), as were adverse events leading to discontinuation of treatment (9.2%, 8.6% and 3.3% respectively) and serious adverse events (8.8%, 8.6% and 6.1% respectively). The most frequently reported were gastrointestinal adverse events (65.2%, 56.2% and 39.2% for liraglutide 3.0 mg, liraglutide 1.8 mg and placebo respectively) such as nausea and vomiting, diarrhoea and constipation and these mainly contributed to the higher rate of withdrawals in the liraglutide groups. Symptomatic hypoglycaemic episodes were also more frequent with liraglutide 3.0 mg (23.0%) and liraglutide 1.8 mg (22.4%) than with placebo (12.7%) particularly in participants taking concomitant sulfonylurea (2.7% treated with liraglutide 3.0 mg and 3.8% treated with liraglutide 1.8 mg, along with background sulfonylurea, experienced severe hypoglycaemic episodes). No statistical analysis was reported for the safety data. The authors state that the safety profile of liraglutide in this study was consistent with prior clinical experience in type 2 diabetes and weight management studies and no new safety signals were identified. No cases of pancreatitis were reported and increased resting heart rate was not dose-dependent, was reversible on treatment cessation and has been observed with other GLP-1 receptor agonists, although the long-term clinical significance of this effect is unknown.
Commentary

Commentary provided by Medicines and Prescribing Programme

The most effective treatment choice for addressing obesity or excess weight is through lifestyle interventions and changing behaviour, although many people find this difficult to do in isolation, even with multifactorial interventions and professional support. It is acknowledged that people with type 2 diabetes find weight loss particularly challenging. The options available for safe and effective pharmacological interventions for weight loss are limited. In this well-designed RCT (Davies et al. 2015) liraglutide 3.0 mg, in combination with diet and exercise, has been shown to be better than placebo for achieving a mean weight loss of more than 5% and over 56 weeks, with the greatest loss seen in the first 20 weeks of treatment. This result is within the parameters that NICE recommends for continued orlistat therapy beyond 3 months. There are other published data that also show some benefits of liraglutide 3.0 mg when compared to placebo for weight loss in people who are obese or overweight but without type 2 diabetes. Additionally there are some limited published data that compare liraglutide 3.0 mg with other pharmacological therapies for weight management such as orlistat in people who were obese. In this study (Astrup et al. 2012) liraglutide 3.0 mg recipients lost 3.8 kg (95% CI 1.6 to 6.0) more weight than those on open-label orlistat (n=95, p≤0.0001, ITT, LOCF) from randomisation to year 1. However a further limitation of all RCTs is the generalisability to real world clinical situations and whether similar weight loss would be achieved without the strictly controlled confines of a clinical trial.

In weighing up the risks and benefits of treatment it is important to note that in the SCALE study statistically significantly more people, particularly at the higher dose of liraglutide, reported adverse events than compared with placebo, including gastrointestinal events and hypoglycaemia. The fact that liraglutide therapy requires a daily subcutaneous injection, with a frequency of injection site events of around 9%, is also a factor that people will need to consider carefully. Long term safety data for liraglutide are still emerging and the authors have stated that this study was underpowered to determine definitive safety conclusions.

Although liraglutide 3.0 mg has received a European marketing authorisation for weight management it is not available in the UK and therefore the likely cost is unknown at present. As with all new medicines, Saxenda has a ‘black triangle’ for the first years after approval and any suspected adverse drug reactions should be reported through the Yellow Card Scheme (see Drug Safety Update, June 2009, on the black triangle scheme for more information). It is important that prescribers do not confuse the new liraglutide product (Saxenda) with the existing liraglutide product (Victoza) as they are licensed for different indications and at different doses.

Study sponsorship

This RCT was funded by Novo Nordisk. Liraglutide is a Novo Nordisk product.

References

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