Randomised controlled trial

Liraglutide for weight loss: more research is needed

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Commentary on: **Astrup A**, Rössner S, Van Gaal L, *et al.* Effects of liraglutide in the treatment of obesity: a randomised, double-blind, placebo-controlled study. *Lancet* 2009;**374**:1606–16.

Obesity is arguably the most important health problem of the developed world in the early 21st century. Despite many attempts to develop safe and effective weight loss medications, the history of pharmacotherapy for obesity is unfortunately littered with failures.[1] Most recently, the finding of higher rates of cardiovascular events in the multi-centre European SCOUT (Sibutramine Cardiovascular OUtcomes Trial) has led the European Medicines Agency to recommend that sibutramine be removed from the market in the EU. Nevertheless, the potential market for weight loss agents is substantial. Glucagon-like peptide-1 (GLP-1) analogues are a new class of agents developed originally for the treatment of type 2 diabetes and noted to produce modest weight loss.[2] Astrup and colleagues tested the second agent in this class, liraglutide, for the treatment of obesity.

The study randomised 564 individuals aged 18–65 years and with a body mass index of 30–40 kg/m^2 to (1) placebo, (2) one of four doses of liraglutide (1.2, 1.8, 2.4 or 3.0 mg, injected once daily) or (3) open-label treatment with orlistat (120 mg tid). The primary outcome was weight loss after 20 weeks. An 84-week open-label extension study followed the 20-week randomised trial, but it is not reported in the paper by Astrup and colleagues. All patients were instructed to follow a low-fat diet, with a 500 kcal/day deficit. Patients with known diabetes were excluded, but approximately 3–4% were found to have diabetes after screening, and an additional 30–31% had pre-diabetes (either impaired fasting glucose or impaired glucose tolerance). From the time of the 2-week dietary run-in period, weight losses in the placebo group, the four liraglutide groups and the orlistat group averaged 2.8, 4.8, 5.5, 6.3, 7.2 and 4.1 kg, respectively. The percentage of patients losing 5% of initial weight was 29.6% in the placebo group, compared with 60.8% and 76.1% in the liraglutide 2.4 and 3.0 mg groups, respectively. Treatment with liraglutide significantly reduced the percentage of patients with pre-diabetes but did not improve blood pressure or lipids. Nausea, vomiting, diarrhoea and fatigue were more common in the liraglutide groups than in the placebo group. The trial by Astrup and colleagues was well done, although it is not clear why treatment with orlistat was open-label during the first 20 weeks: participants could have been provided with matching placebo pills. Also, this study leaves unanswered the suspicion of some obesity experts that it is mainly nausea which leads to weight loss among individuals taking GLP-1 agonists.

What are the implications of this study for clinical practice? The drug appears to meet the US Food and Drug Administration (FDA) criteria for weight loss.[3] The percentage of patients losing ≥5% of initial weight in the two arms with the highest doses of liraglutide was more than twice the percentage in the placebo group, with at least 35% of treated patients losing ≥5% of initial weight. However, the drug does not meet the European Medicines Agency criterion of a loss of ≥10% of initial weight.[4] In addition, FDA guidance states that for safety assessment, trials should randomise approximately 3000 individuals to active drug and 1500 to placebo for at least 1 year.[3] The data from this trial would not be adequate to support an application

for liraglutide as a weight loss agent in either the USA or the EU. (The drug was just approved in January 2010 for treatment of diabetes in the USA.) Thus, additional trials are required before clinicians can prescribe liraglutide for weight loss. Finally, although liraglutide appears to be as effective as currently approved weight loss agents,[5] a difference of 4–5 kg between placebo and treatment groups is unlikely to make liraglutide a blockbuster for weight management. If the drug is approved by regulatory agencies, whether it is widely prescribed will probably depend on other factors, such as cost and patients' willingness to use an injectable therapy for weight loss.

Competing interests AGT has received an unrestricted grant from GlaxoSmithKline Consumer Healthcare for an epidemiological study of obesity and co-morbid medical conditions in the National Ambulatory Medical Care Survey in the USA.

References

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