Liraglutide, a new diabetes treatment approved by NICE

Type 2 diabetes (T2D) is a global epidemic with a significant burden on patients and health care systems.[1] Improving glycaemic control reduces the risk of development and progression of microvascular complications and possibly cardiovascular disease if applied early in the course of T2D.[2,3] Over the last six decades, several pharmacological agents have been developed to improve glycaemic control in patients with T2D. These agents have limitations relating to weight gain (insulin, sulphonylureas, metaglinides and glitazones), hypoglycaemia (insulin, sulphonylureas and metaglinides), oedema (insulin, glitazones), and gastrointestinal side effects (metformin, acarbose). There are also contraindications which limit their use in certain patients such as those with heart failure (glitazones) and renal failure (metformin). Furthermore, they do not produce sustained improvements in glycaemia or reverse the decline in beta-cell function which is responsible for the progressive nature of the disease.

Incretin based therapies are the latest classes of diabetes treatments. There are two main groups: dipeptidylpeptidase-4 (DPP-4) inhibitors (sitagliptin, vildagliptin and saxagliptin) and glucagon-like peptide (GLP-1) analogues (exenatide, liraglutide). DPP-4 inhibitors are given orally, are associated with low risk of hypoglycaemia (unless used with sulphonylureas) and cause no weight gain. GLP-1 analogues are given as daily subcutaneous injection, cause weight loss and are associated with low risk of hypoglycaemia when not used with sulphonylureas.

Liraglutide (Victoza) is a GLP-1 analogue that is licensed by the European Medicines Agency for treatment of adults with T2D in combination with metformin or a sulphonylurea, in patients with insufficient glycaemic control despite maximal tolerated dose of monotherapy with metformin or sulphonylurea or in combination with metformin and a sulphonylurea or metformin and a glitazone in patients with insufficient glycaemic control despite dual therapy.[4] The National Institute for Health and Clinical Excellence (NICE) has recently approved the use of liraglutide in patients with T2D.

Findings from clinical trials

The clinical efficacy of liraglutide was investigated in the phase III LEAD studies (Liraglutide Effect and Action in Diabetes) and the 1860 trial.[5–11] The former consisted of six randomised controlled trials involving more than 4400 patients with T2D, of whom approximately 2700 received liraglutide, from over 600 sites in 40 countries.[12,13] All trials, except LEAD 3 (52 weeks), were of 26-week duration with some having open label extensions.

The LEAD 1 and 2 and the 1860 trials assessed the use of liraglutide as an add-on therapy. In LEAD 1, liraglutide was compared to rosiglitazone or placebo when added to glimepiride.[9] In LEAD 2, liraglutide was compared to glimepiride or placebo when added to metformin.[6] In the 1860 trial, liraglutide was compared to sitagliptin when added to metformin.[11]

LEAD 4, 5 and 6 assessed the use of liraglutide as triple therapy. In LEAD 4, liraglutide was compared to placebo when added to metformin and rosiglitazone.[10] In LEAD 5, liraglutide was compared to insulin glargine or placebo when added to metformin and glimepiride.[7] In LEAD 6, liraglutide was compared to exenatide when both were added to oral diabetes treatments.[8]

Liraglutide (0.6–1.8mg daily) produced significant reductions in HbA_{1c} ranging from -0.7 to -1.5% when used as second or third line therapy.[14] HbA_{1c} reductions were significantly more than placebo or the active comparator in the trials, except in LEAD 2 where liraglutide was non-inferior to glimepiride.[14] Liraglutide (1.8mg) was also superior to exenatide (10µg bd) in LEAD 6 (estimated treatment difference 0.33; 95% CI -0.47 to -0.18; $p<0.0001$).[8] In all trials, liraglutide resulted in significant weight loss (-1.0 to -3.5kg) compared to placebo (except in LEAD 1) or active comparators.[14]

Liraglutide was generally well tolerated with nausea being the most common side effect affecting 14–40% of patients during the initial weeks of treatment but subsiding in most cases thereafter.[13] When added to metformin or a glitazone, liraglutide resulted in hypoglycaemia incidence similar to placebo.[15] Liraglutide caused less hypoglycaemia than glimepiride but combining liraglutide with a sulphonylurea increased the risk of hypoglycaemia.[15]

Approval for use

Based on the above, and cost-effectiveness analysis, NICE has recently approved the use of liraglutide 1.2mg in patients with inadequate glycaemic control (HbA_{1c} ≥7.5% [58mmol/mol]) as part of triple therapy (in combination with metformin and a sulphonylurea, or metformin and a thiazolidinedione) if the patient has a body mass index (BMI) ≥35kg/m^2 (cut-off should take ethnicity into consideration) and specific psychological or medical problems associated with the high BMI, *or* a BMI <35kg/m^2 and where therapy with insulin would have significant occupational implications or weight loss would benefit other significant obesity-related co-morbidities.[16] Liraglutide 1.2mg was also approved to be used in dual therapy in combination with metformin or a sulphonylurea only if the person is intolerant of either metformin *or* a sulphonylurea, or treatment with metformin *or* a sulphonylurea is contraindicated, *and* the person is intolerant of glitazones *and* DPP-4 inhibitors, or treatment with glitazones *and* DPP-4 inhibitors is contraindicated.[16] The 1.2mg dose was recommended as any extra benefits of the 1.8mg dose were not considered to be cost effective.

Many patients with T2D who require a third diabetes agent will have a BMI ≥35kg/m^2 and the majority will have associated medical or psychological conditions related to obesity such as dyslipidaemia, hypertension, obstructive sleep apnoea and osteoarthritis which could be exacerbated by further weight gain. Even in patients with BMI <35kg/m^2, a significant number will have obesity-related complications in which further weight gain is undesirable. Hence, a large proportion of patients with T2D requiring a third line therapy will be eligible for liraglutide treatment. The use of liraglutide as a second line therapy is much more restricted. Patients who are intolerant of multiple oral diabetes treatments will be eligible for liraglutide as a second line therapy. In addition, patients with a history of heart failure and who are at high risk of hypoglycaemia will be eligible to receive liraglutide if not tolerant of DPP-4 inhibitors. Added to this, it might be argued that in those patients with significant co-morbidity (e.g. obstructive sleep apnoea) weight gain would be a contraindication to any medication which causes this. This might exclude addition of sulphonylureas, glitazone or insulin to metformin leaving the only choice second line as a DPP-4 inhibitor or liraglutide. If the co-morbidity is sufficiently severe to make weight loss an imperative, then NICE guidance appears to allow for the use of liraglutide second line in preference to the above agents. This is a matter of interpretation, but NICE guidelines clearly state that it is up to the health professionals in consultation with the patient to do what is best for that individual patient.

Conclusion

Liraglutide appears to be an effective and a well-tolerated GLP-1 analogue for the treatment of T2D. The recent NICE approval positioned liraglutide as a third line agent in most cases or as a second line agent in certain circumstances. It is likely that a large number of patients with T2D who require a third agent (and some of those requiring a second agent) will be eligible to receive liraglutide treatment.

The Association of British Clinical Diabetologists (ABCD) is currently undertaking a nationwide audit of liraglutide usage and would welcome contributions to the data (please refer to website: www.diabetologists.org.uk/liraglutide.htm).

Abd A Tahrani, MD, MRCP, MMedSci
Anthony H Barnett, BSc(Hons), MD, FRCP
School of Clinical and Experimental Medicine, University of Birmingham and Department of Diabetes and Endocrinology, Heart of England NHS Foundation Trust, Birmingham, UK

Conflict of interest statement

AHB has received honoraria for lectures and advisory work from relevant companies including Novo Nordisk, Eli Lilly, Sanofi-Aventis, Roche and GlaxoSmithKline.

AT is a research training fellow supported by the National Institute for Health Research.

The views expressed in this publication are those of the authors and not necessarily those of the NHS, the National Institute for Health Research or the Department of Health. AT has received research grants from Sanofi-Aventis and the Novo Nordisk UK Research Foundation.

References

1. International Diabetes Federation. *IDF Diabetes Atlas,* 4th edn. IDF, 2009. (www.diabetesatlas.org/.)
2. Effect of intensive blood-glucose control with metformin on complications in overweight patients with type 2 diabetes (UKPDS 34). UK Prospective Diabetes Study (UKPDS) Group. *Lancet* 1998; **352**(9131): 854–65.
3. Holman RR, *et al.* 10-Year follow-up of intensive glucose control in type 2 diabetes. *N Engl J Med* 2008; **359**(15): 1577–89.
4. Victoza. European Medicines Agency, 2010. (www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/001026/human_med_001137.jsp&murl=menus/medicines/medicines.jsp&mid=WC0b01ac058001d125.)
5. Garber A, *et al.* Liraglutide versus glimepiride monotherapy for type 2 diabetes (LEAD-3 Mono): a randomised, 52-week, phase III, double-blind, parallel-treatment trial. *Lancet* 2009; **373**(9662): 473–81.
6. Nauck M, *et al.* Efficacy and safety comparison of liraglutide, glimepiride, and placebo, all in combination with metformin, in type 2 diabetes: the LEAD (Liraglutide Effect and Action in Diabetes)-2 study. *Diabetes Care* 2009; **32**(1): 84–90.
7. Russell-Jones D, *et al.* Liraglutide vs insulin glargine and placebo in combination with metformin and sulfonylurea therapy in type 2 diabetes mellitus (LEAD-5 met+SU): a randomised controlled trial. *Diabetologia* 2009; **52**(10): 2046–55.
8. Buse JB, *et al.* Liraglutide once a day versus exenatide twice a day for type 2 diabetes: a 26-week randomised, parallel-group, multinational, open-label trial (LEAD-6). *Lancet* 2009; **374**(9683): 39–47.
9. Marre M, *et al.* Liraglutide, a once-daily human GLP-1 analogue, added to a sulphonylurea over 26 weeks produces greater improvements in glycaemic and weight control compared with adding rosiglitazone or placebo in subjects with type 2 diabetes (LEAD-1 SU). *Diabet Med* 2009; **26**(3): 268–78.
10. Zinman B, *et al.* Efficacy and safety of the human glucagon-like peptide-1 analog liraglutide in combination with metformin and thiazolidinedione in patients with type 2 diabetes (LEAD-4 Met+TZD). *Diabetes Care* 2009; **32**(7): 1224–30.
11. Pratley RE, *et al.* Liraglutide versus sitagliptin for patients with type 2 diabetes who did not have adequate glycaemic control with metformin: a 26-week, randomised, parallel-group, open-label trial. *Lancet* 2010; **375**(9724): 1447–56.
12. McGill JB. Insights from the liraglutide clinical development program – the Liraglutide Effect and Action in Diabetes (LEAD) studies. *Postgrad Med* 2009; **121**(3): 16–25.
13. Raskin P, Mora PF. Glycaemic control with liraglutide: the phase 3 trial programme. *Int J Clin Pract* 2010; **64:** 21–7.
14. Tahrani AA, *et al.* Glycaemic control in type 2 diabetes: targets and new therapies. *Pharmacol Ther* 2010; **125**(2): 328–61.
15. Russell-Jones D. The safety and tolerability of GLP-1 receptor agonists in the treatment of type 2 diabetes. *Int J Clin Pract* 2010; **64**(10): 1402–14.
16. National Institute for Health and Clinical Excellence. Liraglutide. NICE, 2010. (http://guidance.nice.org.uk/TA/Wave20/68.)