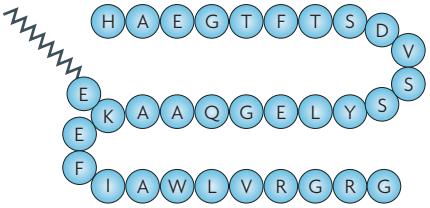
FRESH FROM THE PIPELINE

Liraglutide

Daniel J. Drucker, Argyris Dritselis and Peter Kirkpatrick



In January 2010, liraglutide (Victoza; Novo Nordisk) — an injectable glucagon-like peptide 1 receptor agonist — was approved by the US FDA to improve glycaemic control in adults with type 2 diabetes mellitus.

Type 2 diabetes is a common metabolic disorder that is characterized by insufficient insulin production, often accompanied by defective insulin action. The global prevalence of the disorder is increasing rapidly, largely due to the increasing incidence of obesity.

Although there are more than 10 drug classes available for the treatment of type 2 diabetes, the risk–benefit ratios of many available agents remains suboptimal, thereby complicating treatment choices. The biguanide metformin is widely used as the first-choice treatment[1], but gastrointestinal intolerance may limit its use in up to 15–20% of patients. Sulphonylureas such as glimepiride potently increase insulin secretion, but their use is frequently associated with hypoglycaemia and weight gain, and many patients become resistant to their actions[1]. Thiazolidinediones such as rosiglitazone are effective insulin sensitizers[1]. However, thiazolidinedione therapy may be accompanied by peripheral oedema, weight gain, congestive heart failure and osteoporosis[1]. Insulin therapy is highly effective, but requires frequent self-monitoring of blood glucose, and its use is also associated with weight gain and hypoglycaemia[1].

Basis of discovery

The most recent drug classes to be introduced for type 2 diabetes are based on the activity of two incretin hormones: glucagon-like peptide 1 (GLP1) and glucose-dependent insulinotropic polypeptide (GIP)[2]. These two hormones potentiate glucose-dependent insulin secretion from islet β-cells by activating specific G protein-coupled receptors[2].

One class of drugs enhance the activity of endogenous incretins by inhibiting their normally rapid breakdown by the protease dipeptidyl peptidase 4 (DPP4)[2]. The first DPP4 inhibitor to be approved was sitagliptin (Januvia; Merck) in 2006, and two further such drugs have since been approved: saxagliptin (Onglyza; Bristol–Myers Squibb/AstraZeneca) and vildagliptin (Galvus; Novartis). The second class of incretin-based drugs are agonists of the GLP1 receptor that are resistant to DPP4-mediated degradation[2]. The first such agent to be approved was exenatide (Byetta; Amylin/Eli Lilly) in 2005. It has recently been joined by liraglutide, which received marketing approval in the European Union in July 2009, and approval in Japan and the United States in January 2010.

Drug properties

Liraglutide was discovered during studies of GLP1 derivatives intended to increase the plasma half-life compared with human $GLP1_{7–36amide/7–37}$, which is ~2 min[2,3]. The peptide portion of liraglutide, which is produced recombinantly in yeast, is identical to $GLP1_{7–37}$, except that the lysine at position 34 is substituted by arginine[3,4]. It also has a 16-carbon fatty-acid chain with a glutamic acid spacer, which is chemically attached to the remaining lysine residue at position 26 of the peptide precursor[3,4]. These modifications prolong the plasma half-life of liraglutide to 13 hours following subcutaneous administration, in part by facilitating its binding to plasma proteins[3,4].

Like $GLP1_{7–37}$, liraglutide activates the GLP1 receptor, leading to insulin release in the presence of elevated glucose concentrations, and it decreases glucagon secretion in a glucose-dependent manner[2,4]. The mechanism of blood glucose lowering also involves a delay in gastric emptying[2,4].

Clinical data

The efficacy and safety of liraglutide (administered subcutaneously once daily) were assessed in five double-blind, randomized, controlled clinical trials involving a total of 3,978 patients with type 2 diabetes[4–9]. One trial of the drug as a monotherapy had a duration of 52 weeks, and the other four trials of the drug in combination with one or two other antidiabetic drugs had a duration of 26 weeks[4–9]. Primary efficacy parameters included glycated haemoglobin (HbA1c), an indicator of average blood-sugar levels for the past 3–4 months, and body weight[4–9].

In the 52-week trial of liraglutide as a monotherapy, 746 patients were randomized to receive 1.2 mg or 1.8 mg liraglutide, or 8 mg glimepiride[5]. Treatment with liraglutide at 1.8 mg or 1.2 mg dosages resulted in a significant reduction in HbA1c levels compared with glimepiride; the mean decreases were –1.1%, –0.8% and –0.5%, respectively[5].

In a 26-week trial of liraglutide added to metformin, 1,091 patients were randomized to receive 0.6 mg, 1.2 mg or 1.8 mg liraglutide, placebo or 4 mg glimepiride, all in addition to metformin[6]. Treatment with 1.8 mg or 1.2 mg liraglutide in addition to metformin resulted in a significant reduction in HbA1c levels compared with placebo added to metformin, and in a similar HbA1c reduction to 4 mg glimepiride in addition to metformin[6]. The mean decreases were –1.0%, –1.0%, +0.1% and –1.0%, respectively[6].

In a 26-week trial of liraglutide added to a sulphonylurea, 1,041 patients were randomized to receive 0.6 mg, 1.2 mg or 1.8 mg liraglutide, placebo or 4 mg rosiglitazone, all in addition to glimepiride[7]. Treatment with 1.8 mg or 1.2 mg liraglutide in addition to glimepiride resulted in a significant reduction in HbA1c levels compared with placebo added to glimepiride; the mean decreases were –1.1%, –1.1% and +0.2%, respectively[7].

In a 26-week trial of liraglutide added to metformin and a sulphonylurea, 581 patients were randomized to 1.8 mg liraglutide, placebo or insulin glargine, all in addition to metformin and glimepiride[8]. Treatment with liraglutide in addition to glimepiride and metformin resulted in a significant reduction in HbA1c levels compared with placebo added to glimepiride and metformin[8]. The mean decreases were –1.3% and –0.2%, respectively[8].

In a 26-week trial of liraglutide in addition to metformin and a thiazolidinedione, 533 patients were randomized to receive 1.2 mg or 1.8 mg liraglutide, or placebo, all in addition to rosiglitazone and metformin[9]. Treatment with 1.8 mg or 1.2 mg liraglutide in addition to metformin and rosiglitazone resulted in a significant reduction in HbA1c levels compared with placebo added to metformin and rosiglitazone[9]. The mean decreases were –1.5%, –1.5% and –0.5%, respectively[9].

Liraglutide therapy was consistently associated with mild to moderate weight loss of 1–3 kg in the majority of treated patients[4–9].

Indications

Liraglutide is approved by the FDA as an adjunct to diet and exercise to improve glycaemic control in adults with type 2 diabetes mellitus[4]. ►

ANALYSIS | TYPE 2 DIABETES

Analysing issues in the use of GLP1-targeted drugs for type 2 diabetes is Daniel J. Drucker, M.D., Director, Banting and Best Diabetes Centre, University of Toronto, Canada.

In the past 5 years, two new classes of antidiabetic agents that potentiate the actions of the gut hormone GLP1 have been approved[2]. DPP4 inhibitors, such as sitagliptin, vildagliptin and saxagliptin, prevent the degradation of GLP1 and GIP, and control glucose mainly via the regulation of insulin and glucagon secretion[2]. GLP1 receptor agonists (such as exenatide and liraglutide) stimulate insulin secretion and inhibit glucagon secretion, inhibit gastric emptying, and also promote satiety, leading to control of body weight[2]. DPP4 inhibitors and GLP1 receptor agonists exert their actions in a glucose-dependent manner without weight gain or the need for frequent dose adjustment, which are key features that are often lacking in older antidiabetic drugs.

Although exenatide is an effective therapy when used alone or in combination with other agents, its relatively short half-life necessitates twice-daily administration. Second-generation GLP1 receptor agonists, exemplified by liraglutide, an acylated GLP1 derivative, exhibit a protracted pharmacokinetic profile, making them suitable for once-daily administration. A head-to-head study of liraglutide versus exenatide in subjects with type 2 diabetes demonstrated comparable weight loss with both agents, but liraglutide was better tolerated, and produced a greater reduction in HbA1c levels after 26 weeks of therapy[10]. The next generation of investigational GLP1 receptor agonists promise to be even more convenient and probably more potent[11], with exenatide LAR, taspoglutide and albiglutide all requiring once-weekly administration[2].

However, several questions surrounding the risks and benefits of incretin-based therapy require further investigation[12]. Although GLP1 receptor agonists promote β-cell survival and expand β-cell mass in preclinical studies, evidence for durability of glucose control with prolonged clinical use of these agents has not yet been forthcoming[13]. Continuous GLP1 receptor activation leads to hyperplasia and carcinoma of the calcitonin-producing C cells in rodents, but not in monkeys[14], and calcitonin levels have remained fairly normal with up to 2 years of liraglutide use in patients with diabetes. Nevertheless, the long-term safety of continuous GLP1 receptor activation remains unknown.

Most importantly, however, given the recent concerns over the cardiovascular safety of diabetes drugs, activation of the GLP1 receptor is associated with robust cardioprotection in preclinical studies[15]. In addition, GLP1 receptor agonists promote weight loss, reduce postprandial lipids and blood pressure, and minimize the risk of hypoglycaemia. This raises the possibility that long-term use of these agents may be associated with a reduction in cardiovascular morbidity and mortality independent of their ability to lower blood glucose levels.

With the introduction of liraglutide and other investigational GLP1 receptor agonists in late-stage clinical development, clinicians will soon have many more options for the treatment of type 2 diabetes. However, whether the promise of these new agents will be sustained requires careful study in long-term controlled clinical trials.

Box 1 | The market for antidiabetic drugs

Analysing the market for antidiabetic drugs is Argyris Dritselis, IMS Health, London, UK.

Across the key pharmaceutical markets — the United States, the top five European countries and Japan — the market for antidiabetic drugs was worth US$22.9 billion in 2009, which was a 25.5% growth from 2007 (REF. 16). The United States dominates this market, with reported sales of $15.1 billion, whereas Europe and Japan had reported sales of $5 billion and $2.8 billion, respectively[16].

Human insulin analogues are currently the main drug class in the market, with a 46.1% share, and reported sales of $10.5 billion, followed by thiazolidinediones and DPP4 inhibitors, with sales of $5.5 billion and $2.3 billion, respectively[16]. Sales of DPP4 inhibitors showed a marked ~260% increase over the past three years, whereas sales of thiazolidinediones dropped by 4.5% in the same period[16]. The market (United States and Europe only) for GLP1 analogues was worth $0.75 billion in 2009, a 29% increase from 2007; exenatide (Byetta; Amylin/Eli Lilly), the first-in-class drug, dominated the market with a 98.3% share[16]. The GLP1 analogue liraglutide (Victoza; Novo Nordisk), is the most recent entrant in this emerging market, following its European approval in July 2009 as a second- or third-line treatment for type 2 diabetes in adult patients. In 2010, it was also approved in the United States and in Japan as monotherapy or second-line treatment. Analysts estimate global sales for liraglutide of $262 million in 2010, $1.06 billion in 2013 and a peak of $1.28 billion in 2015 (REF. 17).

Daniel J. Drucker is at the Samuel Lunenfeld Research Institute, Mount Sinai Hospital, 600 University Avenue, TCP5-1004 Toronto, Ontario, Canada M5G 1X5.

Argyris Dritselis is at IMS Health, 7 Harewood Avenue, London NW1 6JB, UK.

Peter Kirkpatrick is at Nature Reviews Drug Discovery.

e-mails: d.drucker@utoronto.ca; ADritselis@be.imshealth.com; p.kirkpatrick@nature.com

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1. Nathan, D. M. *et al.* Medical management of hyperglycemia in type 2 diabetes: a consensus algorithm for the initiation and adjustment of therapy: a consensus statement of the American Diabetes Association and the European Association for the Study of Diabetes. *Diabetes Care* **32**, 193–203 (2009).
2. Lovshin, J. A. & Drucker, D. J. Incretin-based therapies for type 2 diabetes mellitus. *Nature Rev. Endocrinol.* **5**, 262–269 (2009).
3. Knudsen, L. B. *et al.* Potent derivatives of glucagon-like peptide-1 with pharmacokinetic properties suitable for once daily administration. *J. Med. Chem.* **43**, 1664–1669 (2000).
4. US Food and Drug Administration. FDA labelling information — Victoza (liraglutide). *FDA website* [online], http://www.accessdata.fda.gov/drugsatfda_docs/label/2010/022341lbl.pdf (2010).
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* **373**, 473–481 (2009).
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* **32**, 84–90 (2009).
7. 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.* **26**, 268–278 (2009).
8. 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* **52**, 2046–2055 (2009).
9. 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* **32**, 1224–1230 (2009).
10. Buse, J. B. *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* **374**, 39–47 (2009).
11. Drucker, D. J. *et al.* Exenatide once weekly versus twice daily for the treatment of type 2 diabetes: a randomised, open-label, non-inferiority study. *Lancet* **372**, 1240–1250 (2008).
12. Drucker, D. J. *et al.* Incretin-based therapies for the treatment of type 2 diabetes; evaluation of the risks and benefits. *Diabetes Care* **33**, 428–433 (2010).
13. Bunck, M. C. *et al.* One-year treatment with exenatide improves β-cell function, compared with insulin glargine, in metformin-treated type 2 diabetic patients: a randomized, controlled trial. *Diabetes Care* **32**, 762–768 (2009).
14. Knudsen, L. B. *et al.* Glucagon-like peptide-1 receptor agonists activate rodent thyroid C-cells causing calcitonin release and C-cell proliferation. *Endocrinology* 4 Mar 2010 (doi:10.1210/en.2009–1272)
15. Ban, K. *et al.* Cardiovascular consequences of drugs used for the treatment of diabetes: potential promise of incretin-based therapies. *J. Am. Soc. Hyperten.* **3**, 245–259 (2009).
16. IMS MIDAS (IMS Health, 2009).
17. Vosser, R. Hauber, A. & Gordon, J. D. *Europe Equity Research Report* (J. P. Morgan, 5 Feb 2010).

Competing interests statement

D.J.D. declares competing financial interests: see online version for details.