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The safety and efficacy of liraglutide with or without oral antidiabetic drug therapy in type 2 diabetes: an overview of the LEAD 1–5 studies

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Liraglutide is a new glucagon-like peptide-1 (GLP-1) receptor agonist and a true GLP-1 analogue. After successful phase 2 studies, liraglutide was assessed in a series of phase 3 trials [(Liraglutide Effect and Action in Diabetes (LEAD)] designed to demonstrate efficacy and safety across the continuum of type 2 diabetes antihyperglycaemic care, both as monotherapy and in combination with commonly used oral antidiabetic drugs (OADs). The LEAD programme also compared liraglutide with other OADs. As a monotherapy, liraglutide demonstrated significant improvements in glycaemic control in comparison with glimepiride. When combined with one or two OADs, reductions in haemoglobin A1c, fasting plasma glucose and postprandial glucose were generally greater with liraglutide than with comparators. Throughout the trials, liraglutide was associated with weight reduction; in most instances, the reduction from baseline was significantly greater than that seen with comparators. Improvements in assessments of beta-cell function were consistently shown with liraglutide treatment across all trials. Furthermore, reductions in systolic blood pressure were reported. Liraglutide was associated with a low risk of hypoglycaemia and was generally well tolerated. The majority of adverse effects were gastrointestinal, the most frequent of which was nausea.
Keywords: glucagon-like peptide-1, incretin, LEAD studies

Introduction

Incretins, glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP) are gut hormones produced by cells in the gastrointestinal (GI) tract and are secreted into the circulation in response to ingested nutrients. Because of release of these gut hormones, insulin secretion is greater following oral glucose intake than after an intravenous glucose bolus: this phenomenon is known as the 'incretin effect'. It is thought that up to 70% of the insulin response to a meal is mediated through the release of these incretin hormones [1]. The

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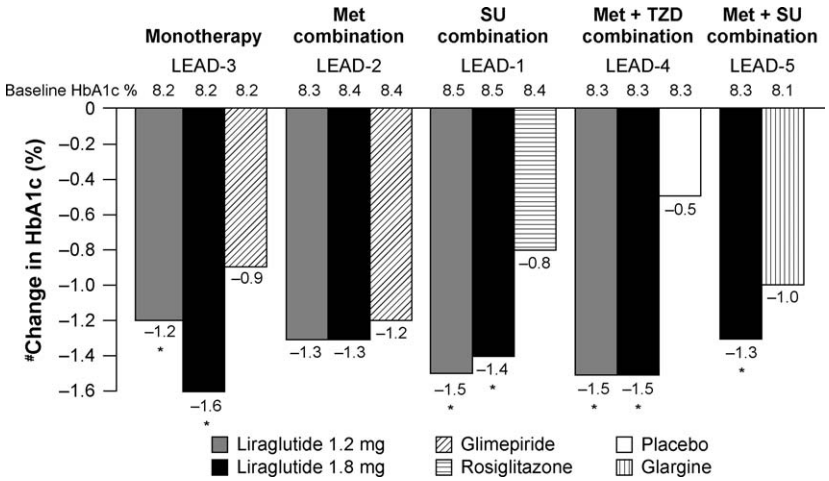

Fig. 1 Change in HbA1c from baseline (LEAD-1 to LEAD-5). *Significant vs. trial comparator. #Change in HbA1c from baseline for overall population (LEAD-4 and LEAD-5), add-on to diet and exercise failure (LEAD-3) or add-on to previous oral antidiabetic drug monotherapy (LEAD-1 and LEAD-2). HbA1c, haemoglobin A1c; LEAD, Liraglutide Effect and Action in Diabetes; Met, metformin; SU, sulphonylurea; TZD, thiazolidinediones.

incretin effect is impaired in people with type 2 diabetes (T2DM), contributing to a blunting of the insulin response to ingested glucose and a failure to appropriately suppress postprandial glucagon levels. These abnormalities are important contributors to the pathophysiology of T2DM, and the deficient incretin response has become an important focus of therapeutic research [2,3].

GLP-1 actions have stimulated interest in its potential use as antihyperglycaemic therapy for T2DM patients. Unfortunately, native GLP-1 has a very short half-life of approximately 2 min because of its rapid degradation in the circulation by dipeptidyl peptidase (DPP)-4 [4], limiting its therapeutic use [5]. While GLP-1 infusions improve glycaemia in T2DM, this is not a practical therapeutic solution.

Two approaches to developing incretin-based therapies are the following: GLP-1 receptor agonists (including exenatide and liraglutide) and DPP-4 inhibitors (including vildagliptin, sitagliptin, saxagliptin and alogliptin). The former relies on subcutaneous administration, which targets GLP-1 receptors but are less susceptible to the enzymatic degradation by DPP-4 than endogenous GLP-1; the latter are oral medications that selectively inhibit the DPP-4 enzyme, resulting in two- to threefold enhancements of endogenous GLP-1 and GIP. GLP-1 receptor agonists enhance insulin secretion and suppress inappropriately elevated glucagon levels, both in a glucose-dependent manner, as well as slow gastric emptying and enhance satiety [6–8]. DPP-4 inhibitors also act to promote insulin secretion and suppress glucagon glucose dependently. However, unlike GLP-1 agonists, DPP-4 inhibitors do not significantly impact gastric emptying or satiety [6–8]. Clinically, both GLP-1 receptor agonists and DPP-4 inhibitors improve glycaemia [9]. GLP-1 agonists are associated with weight loss, whereas DPP-4 inhibitors tend to be weight neutral [9]. Adverse GI symptoms, especially nausea, with GLP-1 agonists are relatively common and tend to be more pronounced early in the course of therapy. GI disturbances are not generally associated with DPP-4 therapy [9].

Exenatide, a synthetic version of exendin-4, was the first GLP-1 agonist to be approved by the Food and Drug Administration (FDA). Exenatide has 53% sequence identity to human native GLP-1 and is partially resistant to DPP-4 degradation, extending its half-life to 2.4 h [10]. Sitagliptin was the first DPP-4 inhibitor to be approved by the FDA in 2006.

Liraglutide is a novel GLP-1 agonist that is a human GLP-1 analogue with an arginine-for-lysine substitution and a C-16 palmitic acid side chain. It has 97% sequence identity to native GLP-1. It has recently been approved by the European Medicines Agency (EMEA) and is awaiting approval from the FDA. Liraglutide's structural modifications result in slower absorption from subcutaneous tissue, reversible albumin binding and resistance to GLP-1 inactivation by DPP-4. Liraglutide is 99% bound to albumin with free liraglutide degraded by endogenous peptidases not through renal elimination [11]. Liraglutide injection produces maximal concentrations in 10–14 h with a half-life of 13 h, making it suitable as a once-daily

injectable treatment for people with T2DM, as an adjunct to lifestyle therapy and in combination with oral antidiabetic drugs (OADs) [12].

The phase 2 development programme demonstrated that liraglutide offers significant improvements in glycaemic control over 14 weeks [13]. In the higher phase 2 trial dose of liraglutide, 1.9 mg, haemoglobin A1c (HbA1c) decreased by 1.45%, while placebo HbA1c increased by 0.29%, which corresponded to a significant between treatment of 1.74% ($p < 0.0001$). This was achieved with significant weight reduction (loss of 2.99 kg, difference of −1.2 kg compared with placebo, $p = 0.0039$) and no major hypoglycaemia as well as reported improvements in beta-cell function of 86% compared with a decline in the placebo group ($p < 0.0001$) [13,14]. Reductions in systolic blood pressure (SBP) were also observed with liraglutide 1.9 mg (−6.63 mmHg) compared with placebo (+1.27 mmHg, between-treatment difference of −7.91 mmHg, $p = 0.0023$) [13]. The potential clinical benefits reported with liraglutide treatment in early trials encouraged its entry into therapeutic confirmatory trials: the Liraglutide Effect and Action in Diabetes (LEAD) phase 3 studies.

LEAD trials included more than 4000 patients recruited at more than 600 sites in 40 countries. It was designed to investigate liraglutide as monotherapy or in combination with various OADs and to compare it with some other antihyperglycaemic therapies commonly used in the treatment of T2DM patients (table 1) [15–20]. Thus, the LEAD programme investigated liraglutide use across the continuum of care of T2DM.

Some trial subjects were at an early stage in the diabetes treatment cascade, having previously been treated with lifestyle measures only or with lifestyle plus not more than half maximal OAD* dose (monotherapy) for at least 2 months prior to liraglutide treatment; the OAD was discontinued before liraglutide treatment commenced (*OADs comprised sulphonylureas, meglitinide, amino acid derivative, biguanide, alpha-glucosidase inhibitors and thiazolidinediones). Other trial subjects were at a more advanced stage of care where they had been receiving two OADs in combination therapy for at least 3 months.

Glycaemic Control Parameters: HbA1c

Liraglutide led to improvements in glycaemic control across the LEAD trials. The two higher doses (1.2 and 1.8 mg) used in the liraglutide monotherapy LEAD-3 study [17] improved glycaemic control from baseline to a significantly greater degree than did glimepiride (figure 1). In addition, HbA1c reductions from baseline were significantly greater with liraglutide 1.8 mg than with 1.2 mg (between-treatment difference of −0.29%, $p = 0.0046$) (figure 1). In the subgroup of patients previously inadequately controlled with diet and exercise alone (the true initial monotherapy population), HbA1c was reduced by 1.6 percentage points with liraglutide

Table 1 Overview of LEAD trials

LEAD study [reference]	Description/baseline data	Comparators	Main treatment	Main comparator
1 [16]	26-week RCT, 1018 patients on a SU, HbA1c: 8.4%, weight: 81.6 kg	Addition of liraglutide 0.6 mg, liraglutide 1.2 mg, liraglutide 1.8 mg, placebo, rosiglitazone 4 mg	Liraglutide + glimepiride	Rosiglitazone + glimepiride
2 [17]	26-week RCT, 1091 patients on metformin, HbA1c: 8.4%, weight: 88.6 kg	Addition of liraglutide 0.6 mg, liraglutide 1.2 mg, liraglutide 1.8 mg, placebo, glimepiride 8 mg	Liraglutide + metformin	Glimepiride + metformin
3 [18]	52-week RCT, 746 OAD-naïve patients, HbA1c: 8.2%, weight: 92.6 kg	Monotherapy: liraglutide 1.2 mg, liraglutide 1.8 mg, glimepiride 8 mg	Liraglutide monotherapy	Glimepiride monotherapy
4 [19]	26-week RCT, 533 patients on metformin + TZD, HbA1c: 8.5%, weight: 97.0 kg	Addition of liraglutide 1.2 mg, liraglutide 1.8 mg, placebo	Liraglutide + metformin + rosiglitazone	Metformin + rosiglitazone
5 [20]	26-week RCT, 581 patients on metformin + SU, HbA1c: 8.2%, weight: 85.4 kg	Addition of liraglutide 1.8 mg, placebo, insulin glargine (dose titrated)	Liraglutide + metformin + glimepiride	Insulin glargine + metformin + glimepiride
6 [21]	26-week RCT, 464 patients on metformin and/or SU, HbA1c: 8.2%, weight: 93 kg	Addition of liraglutide 1.8 mg, exenatide 10 μg	Liraglutide + metformin and/or glimepiride	Exenatide + metformin and/or glimepiride

HbA1c, haemoglobin A1c; LEAD, Liraglutide Effect and Action in Diabetes; OAD, oral antidiabetic drug; RCT, randomized controlled trial; SU, sulphonylurea; TZD, thiazolidinediones.

1.8 mg, and the reduction was sustained throughout the 52-week study period.

Further down the continuum of care, liraglutide used in combination with one or two OADs substantially reduced HbA1c. Liraglutide 1.8 mg in combination with glimepiride (LEAD-1 [15]) reduced HbA1c to a greater degree than placebo or rosiglitazone (figure 1). In the LEAD-2 trial, liraglutide in combination with metformin [16] reduced HbA1c as effectively as glimepiride plus metformin. Liraglutide in combination with two OADs, metformin plus rosiglitazone (LEAD-4 [18]) and metformin plus glimepiride (LEAD-5 [19]) also achieved significant reductions in HbA1c compared with trial comparators (figure 1).

Greater improvements in HbA1c translated into a higher proportion of subjects achieving targets of HbA1c $<7.0\%$ [21] and $\leq 6.5\%$ [22,23] with liraglutide treatment as a monotherapy or when used in combination regimens. For example, 51% of patients treated with liraglutide monotherapy (1.8 mg dose) reached the target HbA1c $<7.0\%$ compared with 28% of patients treated with glimepiride ($p < 0.0001$). Furthermore, 38% of patients reached the target of $\leq 6.5\%$ compared with 16% with glimepiride ($p < 0.0001$). Moreover, a larger proportion of patients reached the HbA1c target of $\leq 6.5\%$ with liraglutide 1.8 mg compared with 1.2 mg (38 vs. 28%, respectively, $p = 0.0208$).

Other Glycaemic Control Parameters

Fasting Plasma Glucose

It is known that both fasting plasma glucose (FPG) and postprandial glucose (PPG) contribute to overall hyperglycaemia and therefore to the risk for micro- and macrovascular diabetic complications in patients with uncontrolled T2DM [24]. Liraglutide used both as monotherapy and as part of a combination regimen has been shown to reduce FPG and PPG. FPG reductions with liraglutide monotherapy were significantly greater compared with glimepiride at both the 1.8 mg and the 1.2 mg doses (figure 2). There was evidence of a dose-dependent effect of liraglutide on FPG, which was more markedly reduced with the 1.8 mg dose than with the 1.2 mg dose.

All three trial doses of liraglutide (0.6, 1.2 and 1.8 mg) in combination with one or two OADs improved FPG; however, compared with the main trial comparators, there was a greater reduction in FPG with the two higher liraglutide doses. For example, FPG reductions observed with liraglutide in combination with glimepiride were significantly greater than placebo at all doses; the 1.2 and 1.8 mg doses, however, produced greater reductions in FPG compared with rosiglitazone plus glimepiride (figure 2) [15]. The reduction in mean FPG in the liraglutide (1.6 mmol/L [28 mg/dL]) and insulin glargine (1.8 mmol/L [32 mg/dL]) groups, and the likelihood of achieving ADA targets ($5 \leq 7.2$ mmol/L [$90 \leq$ FPG ≤ 130 mg/dL]) were comparatively similar and significant vs. baseline and placebo (0.5 mmol/L [9.6 mg/dL]; $p < 0.0001$ for both parameters).

Postprandial Glucose

Liraglutide also reduced PPG across the LEAD trials. When combined with glimepiride, the reduction in PPG with the two higher trial doses of liraglutide (−2.71 mmol/l with 1.8 mg and −2.48 mmol/l with 1.2 mg)

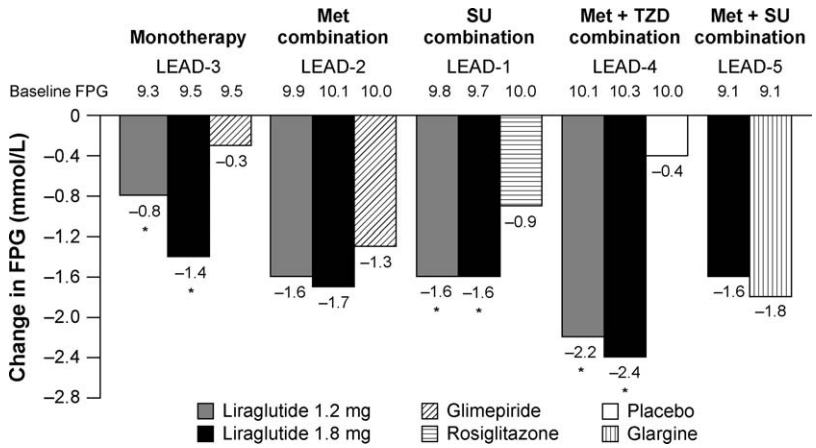

Fig. 2 Mean fasting plasma glucose (FPG) reduction across the LEAD-1 to LEAD-5 trials. *Significant vs. comparator. LEAD, Liraglutide Effect and Action in Diabetes; Met, metformin; SU, sulphonylurea; TZD, thiazolidinediones.

was significantly greater than that with rosiglitazone plus glimepiride (−1.84 mmol/l, p = 0.0022 and p = 0.0434 respectively) [15]. Similarly, a dose-dependent reduction in PPG was also reported with liraglutide in combination with metformin [16]; PPG values significantly decreased from baseline in all liraglutide treatment groups in combination with metformin (−1.68, −2.33 and −2.57 mmol/l for the 0.6, 1.2 and 1.8 mg groups, respectively) compared with −0.62 mmol/l for placebo ($p < 0.001$ for comparisons of all liraglutide groups with placebo). Furthermore, in the LEAD 5 trial, liraglutide 1.8 mg in combination with glimepiride plus metformin was able to reduce PPG to a similar extent as once-daily insulin glargine (−1.81 and −1.6 mmol/l respectively) [19].

Body Weight

Incretin-based therapies have the potential to produce weight loss, unlike many alternative therapies that often lead to weight gain. Liraglutide has consistently offered a significant weight advantage compared with trial comparators. A significant and sustained weight reduction with liraglutide monotherapy (at 1.8 and 1.2 mg) was reported in comparison with glimepiride ($p < 0.0001$ for both) (figure 3). Weight loss with liraglutide monotherapy occurred primarily in the first 16 weeks but was then sustained throughout the 52 weeks of the study [18]. Liraglutide in combination with one or two OADs was also observed to have a significant weight advantage (weight-neutral or weight-loss effect) compared with placebo and to active trial comparators.

Weight loss with liraglutide tends to be dose dependent both in monotherapy and in combination regimens. For example, liraglutide 0.6, 1.2 and 1.8 mg given in combination with metformin over a 26-week period resulted in weight reductions of −1.8, −2.6 and −2.8 kg respectively. These changes were significantly different to the weight gain that occurred when metformin was combined with glimepiride (1.0 kg, $p < 0.0001$) [16]. When combined with metformin plus rosiglitazone, liraglutide at doses of 1.2 and 1.8 mg led to weight reductions of −1.02 and −2.02 kg, respectively, which contrasted significantly with the 0.6 kg weight gain reported with the addition of placebo to metformin and rosiglitazone ($p < 0.0001$ for both comparisons vs. placebo) [18]. Furthermore, in LEAD 5 trial where subjects taking metformin and glimepiride were randomized to receive placebo, insulin glargine or liraglutide, weight loss with liraglutide was greater than that with placebo (Δ 1.4 kg, p = 0.0001) or insulin glargine (Δ 3.4 kg, $p < 0.0001$) [19].

Throughout the LEAD trials, an analysis of change in body weight stratified by body mass index (BMI) (≥30 vs. <30 kg/m^2) demonstrated that there was a greater weight loss in subjects with high BMIs. A substudy of the LEAD 2 trial suggested that the majority of weight loss reported was fat tissue and more likely attributable to visceral adipose tissue loss as demonstrated by dual energy X-ray absorptiometry and computed tomography [25].

Other Clinical Parameters

Systolic Blood Pressure

Liraglutide treatment was associated with reduced SBP. SBP was reduced in a 52-week study by 3.64 mmHg with 1.8 mg of liraglutide given as monotherapy, whereas glimepiride was associated with a small mean increase in SBP (p = 0.0117). Furthermore, the drop in SBP was seen

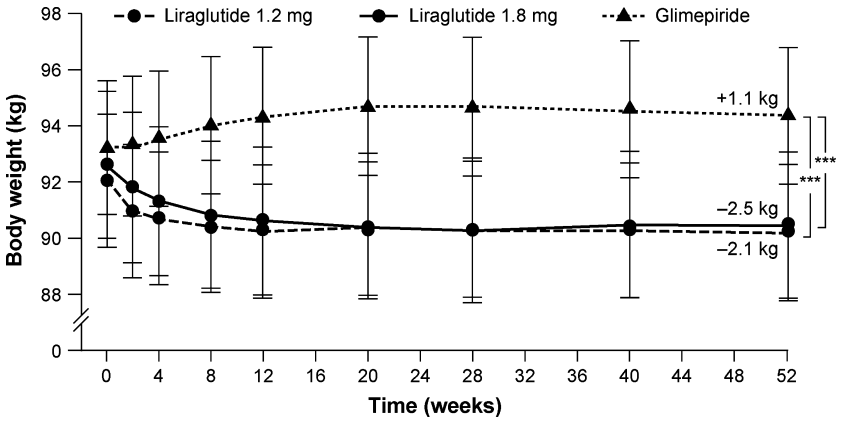

Fig. 3 Change in body weight (kg) from baseline over time (LEAD-3). Copyright of and reprinted with permission from Elsevier: Garber *et al.* [13]. LEAD, Liraglutide Effect and Action in Diabetes.

before weight loss occurred and could therefore be independent of the reduction in weight [17].

Liraglutide has also been associated with SBP reductions when used in combination with an OAD. Subjects receiving liraglutide 1.2 and 1.8 mg, in combination with metformin, had reductions in SBP of 2.29 and 2.81 mmHg respectively. This contrasted with an increase of 0.4 mmHg observed with glimepiride plus metformin (both $p < 0.05$) [16].

Reductions from baseline (approximately 130 mmHg) occurred with both liraglutide 1.2 and 1.8 mg in combination with metformin plus rosiglitazone (−6.7 and −5.5 mmHg, respectively) and were significantly different from placebo (−1.11 mmHg, $p < 0.001$ for both liraglutide groups vs. placebo) [18]. SBP also decreased by 4.0 mmHg from baseline (135 mmHg) with liraglutide 1.8 mg in combination with glimepiride plus metformin compared with a slight increase of 0.54 mmHg reported with the comparator insulin glargine (100 IU/ml once daily, $p < 0.0001$) [19].

Beta-cell Function

Liraglutide has demonstrated an improvement in some assessments of beta-cell function, including such parameters as the homoeostasis model assessment of beta-cell function (HOMA-B) and proinsulin : insulin ratio.

With liraglutide (1.2 and 1.8 mg) in combination with glimepiride, HOMA-B increased significantly compared with glimepiride plus rosiglitazone (table 2) [15,26]. With all liraglutide treatment groups in combination with metformin, improvements of 62–71% in HOMA-B were reported from baseline values of 40–47%. For example, when liraglutide was added to metformin, HOMA-B increased to the same extent as with glimepiride (68%) and significantly greater than that with placebo which demonstrated no change from baseline [16].

Beta-cell function assessments have also improved when liraglutide was combined with two OADs. With liraglutide 1.8 mg in combination with rosiglitazone plus metformin, HOMA-B increased by 27.2 absolute percentage points from a baseline of 34.4%. This was significantly greater than the 5.8% increase from baseline of 39.5% observed with placebo added to rosiglitazone plus metformin ($p < 0.0001$) [19]. HOMA-B also significantly increased by 32.86 absolute percentage points with liraglutide 1.8 mg in combination with glimepiride plus metformin from baseline values of 54.3% in comparison with a slight reduction (−1.14%) with the addition of placebo to glimepiride plus metformin ($p < 0.0001$) [19].

Furthermore, treatment with liraglutide in combination with one or two OADs has demonstrated reductions in proinsulin : insulin ratio. Liraglutide (1.8 and 1.2 mg) in combination with glimepiride resulted in greater reductions in the proinsulin : insulin ratio than glimepiride or placebo (table 2).

A dose-dependent reduction in the proinsulin : insulin ratio was reported when liraglutide was used in combination with metformin plus rosiglitazone, with this ratio decreasing from baseline by 0.085 with 1.8 mg liraglutide and 0.029 with 1.2 mg liraglutide. These reductions were significantly greater than placebo where an increase of 0.036 in the ratio was reported ($p = 0.0004$ vs. liraglutide 1.8 mg, $p = 0.0498$ vs. liraglutide 1.2 mg) (table 2) [22].

Safety and Tolerability

Throughout the LEAD trials, liraglutide has been generally well tolerated, with most adverse events reported to

Table 2 Improvement in assessment of beta-cell function with liraglutide as monotherapy and in combination with one or two OADs (LEAD-1 to LEAD-5) (data from Matthews *et al.* [27])

	LEAD-3 monotherapy	LEAD-2 Met combination	LEAD-1 SU combination	LEAD-4 Met + TZD combination	LEAD-5 Met + SU combination
Proinsulin : insulin					
Liraglutide vs. background	—	−0.12*	−0.09*	−0.12*	−0.10*
Liraglutide vs. comparator	−0.05	−0.03	−0.05*	—	ND
HOMA-B (%)					
Liraglutide vs. background	—	27.75*	34.15	21.40*	34.00*
Liraglutide vs. comparator	TBC	1.44	30.31	—	ND

—, parameters did not apply/were not measured; HOMA-B, homoeostasis model of beta-cell function; LEAD, Liraglutide Effect and Action in Diabetes; Met, metformin; ND, not determined because of cross-reactivity of insulin glargine with assay; SU, sulphonylurea; TZD, thiazolidinediones; Data represent estimated mean differences between treatments (from baseline to end of study).
*$p < 0.03$.

be mild to moderate in severity. GI events (e.g. nausea) were the most frequently reported adverse events with liraglutide monotherapy and combination therapy and were often dose related; 29.3% of patients receiving 1.8 mg liraglutide as monotherapy reported nausea. When liraglutide was used in combination with two OADs, metformin and rosiglitazone, nausea was reported by 40.4% on the higher trial dose of liraglutide (1.8 mg). However, nausea tended to decrease in frequency after 4 weeks in each trial: indeed, in the study by Nauck *et al.*, nausea frequency had declined in incidence to less than 10% by week 4 [16].

In general, serious adverse events were uncommon with liraglutide; for example, in the LEAD 5 trial, patients treated with insulin glargine or placebo reported a 7% frequency of serious adverse events in comparison with a 4% frequency with liraglutide [19].

Antibodies

A relatively low antibody formation against liraglutide across the LEAD studies was reported (8.6%), which is probably related to liraglutide's 97% sequence identity with human native GLP-1 [15–19]. This contrasts with approximately 43% antibody formation reported with exenatide [27]. There were no indications in any of the LEAD studies that antibody formation with liraglutide compromised efficacy.

Frequency of Hypoglycaemia

Liraglutide acts in a glucose-dependent manner; its role in increasing insulin secretion and inhibiting glucagon secretion diminishes as glucose levels become normal and are not present during hypoglycaemia. Therefore, few minor and major hypoglycaemic episodes have been reported with liraglutide across the LEAD studies [28]. For example, as a monotherapy, no major hypoglycaemia incidents were reported and only 8% of patients treated with liraglutide 1.8 mg reported minor hypoglycaemia (plasma glucose <3.1 mmol/l), corresponding to 0.25 episodes/subject-year. In contrast, 24.2% of glimepiride-treated subjects reported minor hypoglycaemia; the rate was $+1.96$ episodes/subject-year ($p < 0.0001$) [28].

Only one major hypoglycaemic episode (blood glucose $=$ 3.0 mmol/l) was reported when liraglutide was used in combination with one OAD. This occurred 9 days after treatment started in a subject receiving liraglutide 1.8 mg in combination with glimepiride. The investigator concluded the event likely to be glimepiride related and thus reduced the dose of the latter from 4 to 3 mg/day. No major hypoglycaemia was reported when liraglutide was used in combination therapy with metformin [15].

The proportion of subjects experiencing minor hypoglycaemia across a 26-week treatment period with liraglutide 1.8 mg in combination with glimepiride was 8.1%, corresponding to 0.47 events/subject-year. This was significantly greater than the proportion of subjects on rosiglitazone in combination with glimepiride (4.3%, 0.12 events/subject-year, $p = 0.0065$). However, the achieved HbA1c was lower in the liraglutide-treated subjects [15].

The incidence of minor hypoglycaemia was lower when liraglutide was used in combination with metformin (approximately 3%), corresponding to a rate of minor hypoglycaemia ranging from 0.03 to 0.14 events/subject-year, across the three doses of liraglutide [16]. Furthermore, the rate of minor hypoglycaemia was low for both liraglutide 1.8 and 1.2 mg in combination with metformin and rosiglitazone (0.64 and 0.38 events/subject-year respectively).

When liraglutide was used in combination with metformin and glimepiride, five patients reported major hypoglycaemia [19]. No medical assistance was required, and the hypoglycaemic events were not reported to be nocturnal. This was in contrast to LEAD-4 trial [18] where no major hypoglycaemic events were reported when liraglutide was used in combination with metformin and rosiglitazone. Major hypoglycaemia with liraglutide seems to occur only when liraglutide is used in combination with a sulphonylurea (one event occurred in the LEAD-1 trial [15]). This may be a result of both agents acting simultaneously to potentiate insulin secretion from beta cells, and the fact that insulin secretion stimulated by sulphonylureas is not glucose dependent. This phenomenon of increased hypoglycaemic risk in combination with a sulphonylurea has also been reported with exenatide [29].

Summary

The LEAD trials have demonstrated the antihyperglycaemic efficacy of liraglutide (1.2 or 1.8 mg daily) in monotherapy and in combination therapy with up to two OADs. Liraglutide provided HbA1c reductions of up to 1.6% across the LEAD-1 to LEAD-5 trials as well as rapid and sustained reductions in FPG and consistent reductions in PPG. Furthermore, improvements in assessments of beta-cell function were observed across the LEAD studies. Liraglutide was also associated with a low risk of hypoglycaemia and in contrast to many other antihyperglycaemic therapies provided significant weight loss throughout the trials. Weight reduction with liraglutide increased with increasing baseline BMI. In addition, liraglutide was found to be associated with a reduction in SBP.

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