Liraglutide in Clinical Practice: Insights from LEAD Programme

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Abstract

The successful management of type 2 diabetes achieves and maintains long-term near-normal glycaemic control. Currently available therapies for type 2 diabetes, including lifestyle modification and pharmacologic intervention, fail to maintain long-term satisfactory glycaemic control, in many cases with a continuous decline in β-cell function. In addition, the risk of hypoglycaemia and weight gain exerts a negative effect on treatment adherence and outcome. There is an unmet medical need for the development of new treatments for type 2 diabetes to obtain a combination of clinical benefits.

Liraglutide, a recently developed glucagon-like peptide-1 (GLP-1) analogue, is a very promising therapeutic option to overcome the limitation of conventional treatments. The efficacy and safety of liraglutide both as mono- and combination therapy with a range of antidiabetic drugs were evaluated in the Liraglutide Effect and Action in Diabetes (LEAD) programme, which covered the entire continuum of care in patients with type 2 diabetes. It included a series of six randomised, controlled phase 3 trials, conducted at more than 600 sites in 40 countries involving more than 4000 patients, of whom approximately 2700 received liraglutide. The LEAD trials clearly demonstrated that once-daily administration with liraglutide led to significant improvements in glycated haemoglobin A₁c (HbA₁c), fasting plasma glucose (FPG) and postprandial glucose (PPG), while reducing body weight and systolic blood pressure (SBP) significantly. Liraglutide was generally well tolerated and was associated with a low rate of hypoglycaemia. Mild, transient nausea was the most commonly reported adverse event.

Overall, liraglutide is effective and safe for long-term administration in patients with type 2 diabetes. Given the additional benefits beyond glycaemic control, such as weight loss, a low risk of hypoglycaemia and the potential for improved β-cell function, early start of liraglutide is recommended.

Introduction

The LEAD programme included a series of six randomised controlled phase 3 trials, which was conducted at more than 600 sites in 40 countries involving more than 4000 patients, of whom approximately 2700 received liraglutide.¹-⁶ Five phase 3a trials (LEAD 1–5) were submitted to regulatory authorities while one phase 3b trial (LEAD 6) was carried out to compare GLP-1 analogues including liraglutide and exenatide. Another phase 3b trial was subsequently completed to compare liraglutide with the dipeptidyl peptidase-4 (DPP-4) inhibitor, sitagliptin, which was not included in the LEAD programme.⁷ The purpose of the LEAD trials was to evaluate the efficacy and safety of liraglutide as mono- or combination therapy in comparison with commonly used treatments of type 2 diabetes (Figure 1). In these trials, the effect of liraglutide on glycaemic control, body weight, β-cell function, blood pressure and lipid profiles were extensively evaluated, as well as its safety and tolerability in patients with type 2 diabetes, which covered a wide scope in the whole spectrum of the treatment of type 2 diabetes.¹-⁶

Design of the LEAD Programme

The primary objective of the LEAD trials was to assess the effect of liraglutide on glycaemic control as measured by change in HbA₁c, in patients with type 2 diabetes.

All trials were randomised, parallel-group, multi-centre trials, in which the efficacy and safety of liraglutide were compared with those of the placebo and/or a specific active comparator (Figure 1). Three different dose levels of liraglutide (0.6 mg, 1.2 mg and 1.8 mg/day) were evaluated. The duration of all LEAD trials was 26 weeks, except LEAD 3, which was 52 weeks (with another three-year extension). Liraglutide was given once daily as monotherapy (LEAD 3), or in combination with one oral antidiabetic drug (OAD) (LEAD 1 and LEAD 2).
Table 1: Demographics summary of LEAD trials

<table>
<thead>
<tr>
<th>Trial</th>
<th>LEAD-3</th>
<th>LEAD-2</th>
<th>LEAD-1</th>
<th>LEAD-4</th>
<th>LEAD-5</th>
<th>LEAD-6</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients randomised (N)</td>
<td>746</td>
<td>1091</td>
<td>1041</td>
<td>533</td>
<td>581</td>
<td>464</td>
</tr>
<tr>
<td>Mean age (yrs)</td>
<td>53.0</td>
<td>56.8</td>
<td>56.1</td>
<td>55.1</td>
<td>57.5</td>
<td>56.7</td>
</tr>
<tr>
<td>Duration of diabetes (yrs)</td>
<td>5.4</td>
<td>7.4</td>
<td>7.9</td>
<td>9.2</td>
<td>9.4</td>
<td>8.2</td>
</tr>
<tr>
<td>Diet and exercise: monotherapy (%)</td>
<td>36 : 64</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

Previously on monotherapy; combination therapy (%)

Mean weight (kg) 98.8 | 88.6 | 81.6 | 96.3 | 85.4 | 93.1 |

Mean BMI (kg/m²) 33.1 | 31.0 | 30.0 | 33.5 | 30.5 | 32.9 |

Mean HbA1c (%) 8.3 | 8.4 | 8.4 | 8.5 | 8.2 | 8.2 |

Mean FPG (mM) 9.5 | 10.0 | 9.8 | 10.1 | 9.2 | 9.6 |

BMI: body mass index; HbA1c: glycated haemoglobin, FPG: fasting plasma glucose.

Overview of LEAD Results

The demographic characteristics of the six LEAD trials are summarised in Table 1. In total, 209 patients from 14 sites in India participated in the LEAD programme.

Glycaemic control

Substantial and sustained reductions in HbA1c were obtained with liraglutide treatment in all LEAD trials across the continuum of care in patients with type 2 diabetes.

Changes in HbA1c from baseline to the end of the trial in all six LEAD trials are summarised in Figure 2.

- Liraglutide as monotherapy: In LEAD-3, the treatment with liraglutide 1.2 mg and 1.8 mg resulted in superior HbA1c reduction compared with glimepiride monotherapy. In a subgroup of patients in LEAD-3, who were previously managed by only diet and exercise, the most pronounced HbA1c reduction from baseline to the end of the trial was observed (liraglutide 1.2 mg: 1.2%; liraglutide 1.8 mg: 1.6%; glimepiride: 0.9%). The percentage of patients reaching HbA1c < 7% or ≤6.5% was significantly higher with both liraglutide doses as compared with glimepiride monotherapy.

- Liraglutide added to one OAD: In LEAD-2, all three liraglutide doses (0.6 mg, 1.2 mg and 1.8 mg) in combination with metformin, resulted in superior HbA1c reduction compared with metformin monotherapy. The 1.2 mg and 1.8 mg liraglutide doses were non-inferior to glimepiride in combination with metformin. The percentage of patients reaching HbA1c < 7% or ≤6.5% was significantly higher with all three liraglutide doses compared with metformin monotherapy, and was similar between the liraglutide and metformin combination therapy group.

- Liraglutide added to two OADs (LEAD 4 and LEAD 5). In LEAD 6, liraglutide or exenatide was also added to one or two OADs.

- Liraglutide head-to-head comparison with exenatide: In LEAD-6, liraglutide resulted in superior HbA1c reduction compared with exenatide head-to-head comparison with exenatide.

- Liraglutide head-to-head comparison with sitagliptin: The treatment with liraglutide 1.2 mg and 1.8 mg added on to metformin resulted in superior HbA1c reduction compared with sitagliptin in combination with metformin. The percentage of patients reaching HbA1c < 7% or ≤6.5% was significantly higher in the two liraglutide groups than in the sitagliptin group.

Rapid and sustained reductions in FPG from baseline to the end of trial were observed with liraglutide (up to −43.2 mg/dL) across the LEAD-1–6 trials. In the LEAD-1, 2, and 4 trials, the significant reduction in FPG from baseline was demonstrated.
within the first two weeks of treatment with liraglutide when in combination with OADs. PPG was also effectively reduced and the mean PPG reduction over three meals was up to −48.6 mg/dL with liraglutide across LEAD trials.\(^4\)

**Body weight**

Significant reductions in body weight were obtained with liraglutide in all LEAD trials.

A very high prevalence of obesity (60–90\%) was found in patients with type 2 diabetes in the U.S.\(^9\) Reducing body weight has been associated with improved glycaemic control, insulin sensitivity and lower risk of coronary heart disease in obese patients with diabetes.\(^10\) Weight gain, a risk factor for cardiovascular disease, is one of the major hurdles in optimising diabetes care with current treatment regimens.\(^11\) In this regard, it is of great importance to develop new treatments for type 2 diabetes with the potential of reducing body weight.

The change in body weight from baseline to the end of the trial was a key secondary endpoint, and the results in all LEAD trials are summarised in Figure 3.

- **Liraglutide as monotherapy:** In LEAD-3, significant reductions in body weight were shown in the liraglutide monotherapy groups, while glimepiride monotherapy resulted in weight gain (weight reduction of 2.1 kg with 1.2 mg, and 2.5 kg with 1.8 mg, weight gain of 1.1 kg with glimepiride monotherapy).
- **Liraglutide added to one OAD:** In LEAD-2, significant reductions in body weight were shown in the liraglutide groups (1.8 kg, 2.6 kg and 2.8 kg with liraglutide 0.6 mg, 1.2 mg and 1.8 mg, respectively), whereas there was a weight gain of 1.0 kg in the glimepiride group.
- **Liraglutide added to two OADs:** In LEAD-4, significant reductions in body weight were shown in the liraglutide groups (1.0 kg with 1.2 mg, and 2.0 kg with 1.8 mg), whereas there was a weight gain of 0.6 kg in the placebo (metformin in combination with glimepiride) group.
- **Liraglutide added to one OAD:** In LEAD-5, the body weight in the liraglutide group was reduced by 1.8 kg, which was significantly greater than in the placebo (metformin in combination with glimepiride) group (0.4 kg). The body weight was increased by 1.6 kg in the insulin glargine group.
- **Liraglutide head-to-head comparison with exenatide:** In LEAD-6, liraglutide and exenatide led to similar reductions in body weight (3.2 kg vs 2.9 kg).
- **Liraglutide head-to-head comparison with sitagliptin:** The reductions in body weight in the liraglutide groups (2.9 kg with 1.2 mg, and 3.4 kg with 1.8 mg) were significantly greater than in the sitagliptin group (1.0 kg).

Clinical meaningful reductions of 2.3 to 6.7 mmHg in SBP with liraglutide have been shown across all LEAD trials.

**Safety**

No major safety concerns with liraglutide were raised in any of the LEAD trials.

The risk of hypoglycaemia is a major concern for both physicians and patients when glycaemic control needs to be intensified with currently available treatments of type 2 diabetes.

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**Table 2: Safety summary of LEAD trials**

<table>
<thead>
<tr>
<th>Trial</th>
<th>Patients randomised (N)</th>
<th>Hypos - major (events per patient year)</th>
<th>Hypos -minor (events per patient year)</th>
<th>Nausea (%)</th>
<th>Withdrawals due to nausea, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>LEAD-3</td>
<td>Liraglutide 1.2 mg</td>
<td>251</td>
<td>0.30</td>
<td>27</td>
<td>9 (4)</td>
</tr>
<tr>
<td></td>
<td>Liraglutide 1.8 mg</td>
<td>247</td>
<td>0.25</td>
<td>29</td>
<td>5 (2)</td>
</tr>
<tr>
<td></td>
<td>Glimepiride 8 mg</td>
<td>248</td>
<td>1.96</td>
<td>9</td>
<td>0</td>
</tr>
<tr>
<td>LEAD-2</td>
<td>Liraglutide 1.2 mg</td>
<td>241</td>
<td>0.03</td>
<td>16</td>
<td>9 (4)</td>
</tr>
<tr>
<td></td>
<td>Liraglutide 1.8 mg</td>
<td>242</td>
<td>0.09</td>
<td>19</td>
<td>15 (6)</td>
</tr>
<tr>
<td></td>
<td>Glimepiride 4 mg</td>
<td>244</td>
<td>1.23</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Placebo</td>
<td>122</td>
<td>0.13</td>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td>LEAD-1</td>
<td>Liraglutide 1.2 mg</td>
<td>228</td>
<td>0.51</td>
<td>11</td>
<td>5 (2)</td>
</tr>
<tr>
<td></td>
<td>Liraglutide 1.8 mg</td>
<td>234</td>
<td>0.009</td>
<td>0.47</td>
<td>7 (2)</td>
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<tr>
<td></td>
<td>Rosiglitazone 4 mg</td>
<td>232</td>
<td>0.12</td>
<td>3</td>
<td>0</td>
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<tr>
<td></td>
<td>Placebo</td>
<td>114</td>
<td>0.17</td>
<td>2</td>
<td>0</td>
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<tr>
<td>LEAD-4</td>
<td>Liraglutide 1.2 mg</td>
<td>178</td>
<td>0.4</td>
<td>29</td>
<td>3 (1.7)</td>
</tr>
<tr>
<td></td>
<td>Liraglutide 1.8 mg</td>
<td>178</td>
<td>0.6</td>
<td>40</td>
<td>16 (9)</td>
</tr>
<tr>
<td></td>
<td>Placebo</td>
<td>177</td>
<td>0.2</td>
<td>9</td>
<td>0</td>
</tr>
<tr>
<td>LEAD-5</td>
<td>Liraglutide 1.8 mg</td>
<td>232</td>
<td>0.056</td>
<td>1.2</td>
<td>14 (2)</td>
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<tr>
<td></td>
<td>Glargine 4 mg</td>
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<td>0.3</td>
<td>1</td>
<td>0</td>
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<tr>
<td></td>
<td>Placebo</td>
<td>115</td>
<td>1.0</td>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td>LEAD-6</td>
<td>Liraglutide 1.8 mg</td>
<td>233</td>
<td>1.93</td>
<td>26</td>
<td>14 (6)</td>
</tr>
<tr>
<td></td>
<td>Exenatide 20 μg</td>
<td>231</td>
<td>0.02</td>
<td>2.60</td>
<td>28 (16)</td>
</tr>
</tbody>
</table>

*significant vs. comparator; MET: metformin; SU: sulphonylurea; TZD: thiazolidinedione

Fig. 3: Change in body weight from baseline in LEAD trials
Liraglutide 1.2 mg is superior (†† p<0.0001)
Liraglutide 1.8 mg is superior (*p<0.01; ** p<0.0001)

percentages were significantly higher than that with all other

LEAD trials.

to other agents from standard classes of antidiabetic therapy in

5 acute cases with liraglutide treatment) was consistent with

the whole, the rate of pancreatitis in the LEAD trials (<0.2%,

with the liraglutide treatment in primates or in humans.19 Acute

pancreatitis has been suggested as a rare side effect of exenatide.

C cells of the thyroid was an active receptor.19 However, there

results obtained in rodents indicated that the GLP-1 receptor in

A relatively low rate of liraglutide antibodies was observed

in LEAD trials, which is due to the high amino acid sequence

homology with native human GLP-1.18 The preclinical study

induced gastrointestinal disorders, it occurred
during the first month of therapy.

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homology with native human GLP-1.18 The preclinical study

results obtained in rodents indicated that the GLP-1 receptor in

C cells of the thyroid was an active receptor.19 However, there

was no evidence of C-cell activation or elevated calcitonin levels

with the liraglutide treatment in primates or in humans.19 Acute

pancreatitis has been suggested as a rare side effect of exenatide.20-

21 In patients with type 2 diabetes, the risk of pancreatitis is

about three times higher than in the general population.22 On

the whole, the rate of pancreatitis in the LEAD trials (<0.2%,

5 acute cases with liraglutide treatment) was consistent with

the expected rate for patients with type 2 diabetes.14 No causal

relationship between liraglutide treatment and pancreatitis could

be established because of the small number of cases in LEAD

trials. Overall, it was considered that liraglutide was safe for

human administration for chronic type 2 diabetes.

Composite endpoint

The comprehensive management of type 2 diabetes not only

focuses on glycaemic control but also includes optimal control

of body weight, hypertension and dyslipidaemia. To better

evaluate the effects of liraglutide treatment on this multifactorial

disease, meta-analysis has been carried out with the data from

LEAD-1–6 trials. A composite endpoint reflecting a broad

measure of diabetes control including HbA1c < 7.0%, no weight

gain and no hypoglycaemia was applied to compare liraglutide

to other agents from standard classes of antidiabetic therapy in

LEAD trials.

This composite endpoint was achieved by 32% and 39% of

patients with liraglutide 1.2 mg and 1.8 mg, respectively. The

percentages were significantly higher than that with all other

comparators (24% with exenatide, 15% with insulin glargine, 8% with

glimepiride, 8% with placebo and 6% with rosiglitazone) (Figure 4). This finding indicates that in comparison with various
currently available antidiabetic agents, liraglutide can definitely
bring more benefits to subjects with type 2 diabetes.

The Place of Liraglutide Therapy in Type 2 Diabetes

The successful management of type 2 diabetes achieves and
maintains long-term near-normal glycaemic control, which
reduces the risk of developing late diabetic complications and
delays the progression of existing complications.23-24 The

treatment modalities currently available for the treatment of
type 2 diabetes include lifestyle modification and pharmacologic
intervention. Because the disease is induced by the continuous
decline in β-cell function, existing therapies will eventually fail
to maintain a long-term satisfactory glycaemic control in most

patients. Furthermore, an increased risk of adverse treatment
effects, such as hypoglycaemia and weight gain, remains a

serious problem for patients treated with OADs and insulin. The

ideal therapy for type 2 diabetes would combine all clinical

benefits, such as adequate glycaemic control, lowering the risk

of hypoglycaemia, improving β-cell function and reducing
diabetes associated morbidity (i.e., obesity, hypertension and

hyperlipidaemia). Hence, there is an unmet medical need for

the development of new treatment for type 2 diabetes.

Taking safety and the quality of glycaemic control

into consideration, the American Association of Clinical

Endocrinologists/American College of Endocrinology (ACE/ ACE)
published a consensus statement to assist primary care

physicians, endocrinologists and other health care providers in

the management of type 2 diabetes.25 Compared to the guidelines

from the American Diabetes Association and the European

Association for the Study of Diabetes (ADA/EASD),24 in which

SUs and insulin are emphasised as well-validated core therapies

added on to lifestyle management and metformin, early use

of the incretin-based therapies, the GLP-1 analogues and the

DPP-4 inhibitors is recommended. The benefits of incretin-based

therapies observed in a wide range of clinical studies support a

preference for utilising these new treatments in clinical settings.

In the therapeutic algorithm from the AACE/ACE, GLP-1

analogues are more favoured than DPP-4 inhibitors, since a better

glycaemic control and a more impressive effect in reducing body

weight is associated with the former.25

From the LEAD trials, it was shown that liraglutide was
effective, safe and well tolerated across the continuum of care

in patients with type 2 diabetes.1-6 Liraglutide can be used

as monotherapy after the failure of diet and exercise, added
to existing metformin therapy or combined with metformin

and thiazolidinedione (TZD) and may also be added to SU

or combined metformin and SU. Currently, only two GLP-1

analogues, liraglutide and exenatide, are available. Greater

improvements in glycaemic control and tolerance were obtained

with liraglutide (administered once daily) than with exenatide

(administered twice daily).1

In India, liraglutide is approved for use in type 2 diabetes as
monotherapy, as well as in combination with other antidiabetic
agents, such as metformin, SUs and TZDs.

Conclusions

Liraglutide, as mono- or combination therapy with a range
of antidiabetic drugs, can lead to significant improvements in HbA1c, FPG and PPG, while reducing body weight and SBP significantly. Liraglutide is generally safe and well tolerated, and associated with a low rate of hypoglycaemia with mild, transient nausea as the most commonly reported adverse event. A relatively low rate of liraglutide antibodies was observed in the LEAD trials. Early liraglutide treatment is recommended to fully achieve its potential benefits.

Acknowledgements

The authors wish to thank Chen Lei, Novo Nordisk, International Operations Clinical Development Center for medical writing support.

References