

A Clinician's Perspective on Liraglutide in Clinical Practice



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Abstract

There is an unmet need for a therapy with comprehensive clinical benefits, including excellent clinical efficacy and safety profiles, while controlling other common coexisting risk factors for the successful management of type 2 diabetes.

Liraglutide, as supported by data from the LEAD programme and a series of case reports, provides a new treatment option for type 2 diabetes with an ideal treatment profile. This includes efficacy in glycaemic control, reductions in body weight and blood pressure, a low rate of hypoglycaemia and improvements in β -cell functions, all of which were confirmed in the LEAD programme and illustrated by case reports. Liraglutide is easy to inject and a flexible treatment for type 2 diabetes that can be readily incorporated into patients' daily lives. Common side effects such as nausea and diarrhoea are usually transient and can be minimised with appropriate administration strategies.

Adequate and open communication with patients about the benefits and side effects of liraglutide therapy are crucial at the initiation of liraglutide treatment. A comprehensive diabetes care plan, including lifestyle modifications, a diabetic education programme, the setting of practical goals of glycaemic control, and regular monitoring on the status of diabetes and its complications, is important to enhance therapy adherence and to obtain the maximal benefits from liraglutide administration.

Introduction

Selecting and optimising treatment of type 2 diabetes is challenging since a balance must be obtained between the maintenance of good glycaemic control and patient safety.¹ With the progression of the disease due to a continuous decline in β -cell function,² a long-term satisfactory glycaemic control is very difficult to maintain with currently available therapies. Along with the disease progression, constant monitoring of blood glucose levels and the adjustment of treatment over time are required.³ Given the co-morbidities that coexist with type 2 diabetes, such as hypertension, dyslipidemia, cardiovascular diseases and obesity, a comprehensive treatment plan is needed for the management of the disease.⁴ Furthermore, various factors such as patients' needs, concerns, capabilities, compliance as well as their welfare support systems should be taken into consideration while individualising therapy. The achievement of beneficial clinical outcomes in diabetes also depends on patient education and monitoring to improve the adherence to treatment.⁵

The first-line therapy widely accepted for type 2 diabetes includes lifestyle modification combined with metformin treatment. However, there is a lack of consensus with regard to which add-on agent to metformin will optimise glycaemic control, given the progress of type 2 diabetes.⁶ Current treatment guidelines from the American Diabetes Association and the European Association for the Study of Diabetes (ADA/EASD) recommend the use of sulphonylureas (SUs) and insulin to be added to lifestyle management and metformin when glycaemic control deteriorates.⁷ The treatment with oral antidiabetics (OADs) and/or insulin often leads to an increased risk of hypoglycaemia and weight gain, which is a major hurdle for treatment adherence. There is an unmet medical need for the development of new treatments for type 2 diabetes, which need to provide a combination of clinical benefits, including long-term glycaemic control and improvement in β -cell function, with a low risk of hypoglycaemia and weight gain. In this regard, early use of the glucagon-like peptide-1 (GLP-1) receptor agonists has been suggested by the American Association of Clinical Endocrinologists/American College of Endocrinology (AAACE/ACE).⁸ The efficacy and safety of liraglutide have been confirmed in the phase 3 clinical development programme, the Liraglutide Effect and Action in Diabetes (LEAD) programme. To obtain optimal therapeutic benefits from liraglutide treatment, a comprehensive treatment plan,

adequate communications to patient at initiation, appropriate goal setting and strategy to enhance therapy maintenance are crucial in clinical practice.

A Case Study Based on LEAD Trial Experience

Mr A., a 57-year-old man, has a height of 185 cm, weight of 111.2 kg with a body mass index (BMI) of 32.5 kg/m². He was diagnosed with type 2 diabetes 12.5 years before the enrollment to the LEAD trials. He had had hypertension for 39 years, diabetic neuropathy for 2 years as well as dyslipidemia. He was treated with 2000 mg metformin alone for diabetes before participating in the trial. He was enrolled in the double-blind LEAD-2 trial and treated with liraglutide 1.2 mg/day in combination with metformin 2000 mg/day. After 26 weeks' treatment with liraglutide, glycated haemoglobin A_{1c} (HbA_{1c}) was reduced from 10.6% at baseline to 6.4% at the end of the trial. Blood pressure was reduced from 144/97 mmHg at baseline to 119/82 mmHg at the end of the trial. Body weight was reduced by 15.3 kg, and BMI was reduced by 4.5 kg/m². The proinsulin-to-insulin ratio was decreased from 0.28 at baseline to 0.13 at the end of the trial, and the homeostatic model for assessment of β -cell function (HOMA-B) was increased from 26% at baseline to 94% at the end of the trial. The treatment with liraglutide not only reduced the HbA_{1c} level significantly, but also led to prominent improvements in body weight and blood pressure, which would significantly reduce the risk of further development of other diabetes-associated complications. The patient had nausea at the beginning of the treatment, then the symptom disappeared within 7 days. There were no reports of any hypoglycaemic events, either mild or severe, during the entire course of study.

Patients such as Mr A. represent a common experience with liraglutide treatment in the management of type 2 diabetes. Liraglutide has been shown to be effective and safe in patients inadequately controlled with lifestyle modifications and OADs. Additional benefits such as reductions in body weight, the number of hypoglycaemic events and systolic blood pressure (SBP) as well as the improvement in β -cell function can also be observed. The LEAD trials have clearly demonstrated that good glycaemic control can be achieved with liraglutide administration either in monotherapy (with lifestyle modification) or in combination with other OADs.⁹ However, more clinical experience will be needed before the full clinical benefits of liraglutide are part of successful diabetic management.

Communication to Patients at the Initiation of Liraglutide Treatment

Adequate and open communication with patients about the

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benefits and side effects of liraglutide therapy are crucial at the initiation of liraglutide treatment. Liraglutide is the first once-daily human GLP-1 analogue for patients with type 2 diabetes. It helps to regulate glucose metabolism in a glucose-dependent manner by stimulating insulin secretion from β cells, and by suppressing glucagon release. Due to the unique action mechanism, treatment with liraglutide does not increase the risk of hypoglycaemia as compared to other current therapies, especially insulin secretagogues and insulin.¹⁰ In addition to significant and sustained benefits in glycaemic control, once-daily administration of liraglutide can also result in clinically meaningful reduction in body weight and SBP, which in turn may reduce the risk of cardiovascular disease (CVD).¹¹ Furthermore, it improves β -cell function in humans, which may potentially delay the inevitable progressive changes in type 2 diabetes.¹²

The most common side effects associated with liraglutide treatment are gastrointestinal disorders such as nausea and diarrhoea. But they are usually transient and disappear after the first few weeks of liraglutide administration.¹³ These symptoms may be alleviated by gradual dose escalation of liraglutide. Less common adverse events include headache, vomiting, dyspepsia, upper abdominal pain, constipation, gastritis, flatulence, abdominal distension, gastroesophageal reflux, bronchitis, nasopharyngitis, dizziness, fatigue, pyrexia, decreased appetite and hypoglycaemia.¹³ In general, liraglutide treatment is associated with a low risk of hypoglycaemia. The risk of hypoglycaemia might increase when liraglutide is co-administered with SU, which can be resolved by reducing the dose of SU.

Liraglutide is administered independent of meals, with an easy-to-use pre-filled pen and 32-gauge fine needles with a length of 8 mm. It can be administered once daily independently of meals, and the injection timing can be changed without dose adjustments, which allows additional treatment flexibility. Furthermore, simple initiation and dose escalation are additional advantages with liraglutide treatment. Based on the dosing guidelines and dose escalation steps derived from the LEAD trial protocols and results, the recommended starting dose of liraglutide is 0.6 mg once daily for at least 1 week to establish tolerability, and then the dose can be escalated to 1.2 mg once daily.¹³⁻¹⁴ The maximum efficacy can be obtained by increasing the dose to 1.8 mg once daily after at least another week. Doses above 1.8 mg daily are not recommended.¹³ However, the clinical administration of liraglutide, including dose and titration, should be individualised at the physician's discretion and be based on the disease status and medical history of patients. Blood glucose monitoring is not required while adjusting the dose, except when liraglutide treatment is combined with an SU. This contributes to a reduction in the cost of blood glucose monitoring.

Goal Setting and Liraglutide Treatment Adherence

A comprehensive diabetes care plan, including lifestyle modifications, a diabetic education programme, the setting of practical goals of glycaemic control and regular monitoring on the status of diabetes and its complications, is often needed to achieve maximum clinical benefit and outcome of treatment.^{1,7,15}

Upon diagnosis, the diabetes care plan and self-management of it should be individualised according to the patient's personal needs, concerns, challenges and capabilities.¹⁶ The diabetes care plan should be reviewed regularly and adjusted according to the evolution of the disease, to ensure continued maintenance of good glycaemic control.¹

When initiating liraglutide treatment, as with other diabetic therapies, setting practical goals for good glycaemic control is important for patient self-management. A step-wise approach should be recommended for the setting of goals (i.e., several short-term goals are set as milestones in order to facilitate and ensure patients achieve the final goal). Furthermore, feedback of treatment outcomes and encouragement of treatment adherence from physicians are

essential to motivate patients to achieve these goals step by step towards long-term successful self-management.⁵

Conclusions

The efficacy and safety of liraglutide were confirmed in the LEAD programme and illustrated by case reports.¹⁰ To maintain a better adherence of liraglutide treatment and to obtain the greatest benefits from the therapy, a comprehensive treatment plan and adequate patient education and monitoring are needed. In addition, proactive interaction between physicians and patients, including positive feedback and appropriate adjustment of strategy at each visit are fundamental to support and motivate patients to achieve the glycaemic control goals.

In conclusion, currently available agents neither maintain long-term satisfactory glucose-lowering efficacy nor exhibit excellent tolerability or safety. Moreover, they fail to reduce the risk of common coexisting complications of diabetes. Although the efficacy of insulin, SUs and thiazolidinediones (TZDs) have been shown in clinical trials and clinical practice, intensive use of these agents is considered to be associated with hypoglycaemia, weight gain and poor adherence.^{7,15} These unmet medical needs shed light on the promising future of liraglutide for the treatment of type 2 diabetes. Liraglutide provides a new treatment option for the disease with comprehensive clinical benefits, including evident efficacy in glycaemic control and additional advantages of reduction in body weight and blood pressure, a low rate of hypoglycaemia and improvements in β -cell functions. It has a considerable potential with the ideal profile of diabetes treatment, which can enable the intensification of therapy, improve the therapy adherence, reduce the rate of coexisting disease risk factors and delay the natural progression in the pathophysiology of type 2 diabetes mellitus (T2DM).

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References

- Peterson GE. A checklist approach to selecting the optimal treatment regimen for a patient with type 2 diabetes. *J Fam Pract* 2009;58(9 Suppl Treating):S21-5.
- Treating patients with type 2 diabetes: what is after lifestyle management and metformin? A focus on the glucagon-like peptide-1 receptor agonists. *J Fam Pract* 2009;58(9 Suppl Treating):S19-20.
- McGill JB. Selecting among ADA/EASD tier 1 and tier 2 treatment options. *J Fam Pract* 2009;58(9 Suppl Treating):S26-34.
- Pollom RD. Importance of daily plasma glucose control in type 2 diabetes. *J Fam Pract* 2009;58(8 Suppl):S10-7.
- Haines ST. Patient education and monitoring recommendations for the use of glucagon-like peptide-1 receptor agonists. *J Fam Pract* 2009;58(9 Suppl Treating):S44-8.
- Drucker DJ, Sherman SI, Gorelick FS, Bergenstal RM, Sherwin RS, Buse JB. Incretin-based therapies for the treatment of type 2 diabetes: evaluation of the risks and benefits. *Diabetes Care* 2010;33:428-33.
- Nathan DM, Buse JB, Davidson MB, Heine RJ, Holman RR, Sherwin R, et al. Management of hyperglycemia in type 2 diabetes: A consensus algorithm for the initiation and adjustment of therapy: a consensus statement from the American Diabetes Association and the European Association for the Study of Diabetes. *Diabetes Care* 2006;29:1963-72.
- Rodbard HW, Jellinger PS, Davidson JA, Einhorn D, Garber AJ, Grunberger G, et al. Statement by an American Association of Clinical Endocrinologists/American College of Endocrinology consensus panel on type 2 diabetes mellitus: an algorithm for glycemic control. *Endocr Pract* 2009;15:540-59.
- McGill JB. Insights from the Liraglutide Clinical Development Program--the Liraglutide Effect and Action in Diabetes (LEAD) studies. *Postgrad Med* 2009;121:16-25.
- Madsbad S. Liraglutide Effect and Action in Diabetes (LEAD) Trial. *Expert Rev Endocrinol Metab* 2009;4:119-29.
- Lovshin JA, Drucker DJ. Incretin-based therapies for type 2 diabetes mellitus. *Nat Rev Endocrinol* 2009;5:262-9.
- Russell-Jones D. Molecular, pharmacological and clinical aspects of liraglutide, a once-daily human GLP-1 analogue. *Mol Cell Endocrinol* 2009;297:137-40.
- Victoza® (liraglutide) Summary of Product Characteristics, July 2009. Available at: <http://emc.medicines.org.uk/medicine/21986/SPC/Victoza+6+mg+ml+solution+for+injection+in+pre-filled+pen/>. Accessed 09 July 2009.
- Victoza® (liraglutide [rDNA origin] injection), solution for subcutaneous use Initial U.S. Approval: 2010. Label approved by FDA, NDA no. 022341. http://www.accessdata.fda.gov/drugsatfda_docs/label/2010/022341lbl.pdf.
- Odegard PS, Capoccia K. Medication taking and diabetes: a systematic review of the literature. *Diabetes Educ* 2007;33:1014-29.
- Funnell MM, Brown TL, Childs BP, Haas LB, Hosey GM, Jensen B, et al. National standards for diabetes self-management education. *Diabetes Care* 2009;32 Suppl 1:S87-94.