

The Promise of Liraglutide in Type 2 Diabetes Mellitus

Tarek Elshourbagy*

Faculty of Medicine-Cairo University, Egypt

***Corresponding Author:** Tarek Elshourbagy, Faculty of Medicine-Cairo University, Egypt.

Received: September 13, 2019; **Published:** September 20, 2019

DOI: 10.31080/ASPS.2019.03.0401

Abstract

Diabetes mellitus (DM) is a chronic medical condition which is characterized by hyperglycemia. It has very serious acute complications such as Diabetic Ketoacidosis (DKA) and Hyperosmotic Hyperglycemic Non ketotic Syndrome (HHNS). Also it has serious long term complications such as macroangiopathies, microangiopathies, neuropathies and others. Many drugs have been developed to combat this disease. However, it remains controlled in fewer than 50% of patients in the U.S [1]. The Incretin mimetics as Liraglutide are new agents which show great results in DM type 2. In this article we will discuss the mechanisms of action, types, outcome and adverse effects of Liraglutide.

Keywords: Liraglutide; Diabetes Mellitus; Type 2

Introduction

Diabetes mellitus (DM) is one of the most common and serious metabolic disorders and probably one of the oldest diseases known to human; it was first described in Egyptian manuscript about 3000 years ago [2]. There are two types of DM; type 1 in which the pancreas fails to produce Insulin and type 2 in which there is Insulin resistance and decreased Insulin sensitivity. It is estimated that 366 million people had DM in 2011. By 2030 this would have risen to 552 millions. DM caused 4.6 million death in 2011 [3].

Although many drugs are available for managing DM type 2, it remains controlled in fewer than 50% of people in the U.S [1], hence more efforts are needed to achieve the recommended ADA and AAACE HbA1c goals below 7% and 6.5% respectively.

The Incretin mimetics is a class of medications which was introduced to the market in 2005 as Exenatide [4]. Liraglutide was approved by the FDA in January 2010 as an adjuvant to diet and exercise in adults with type 2 DM [5].

Mechanisms of action

Liraglutide is a GLP-1 analogue with 97% amino acids sequence homology to GLP-1. It works on GLP-1 receptors in Beta and Alpha cells in pancreatic islets. These receptors are coupled to the enzyme Adenylate Cyclase; this causes increase in cAMP, activation of Protein Kinase A and increase in Calcium level [6] to stimulate the glucose dependent release of Insulin and inhibit the glucose dependent release of Glucagon [7]. Many studies showed that Liraglutide can control glucose level via slowing gastric emptying [8] and increase satiety through activation of different areas in the hind brain and probably via preserving free Leptin level [9]. This could be attributed to the weight loss which occurs with usage of Liraglutide, hence recent studies recommend using it for Obesity [8,9].

Experiments were carried out on animal models and revealed that Liraglutide stimulates beta cell proliferation and pancreatic islet neogenesis. It also protects pancreatic beta cell line (BTC-6 cells) against apoptosis [10].

Figure 1**Types of liraglutide**

Low dose: VICTOZA 1.2mg Injection

High dose: SAXENDA 3MG 15

Clinical effects of liraglutide**Improvement of glycemic control**

Liraglutide has been tried out as monotherapy and HbA1c reduced from baseline by 0.84% with daily doses of 1.2 mg and by 1.14% with daily dose of 1.8 mg [11].

A clinical trial was carried out in diabetic patients with high CVS risk taking Liraglutide and it showed reduction of HbA1c by 0.40% after 36 months of treatment (CI=0.45%-0.34%) with decreased risk of hypoglycemia in Comparison with patients who received Placebo [12].

Another clinical trial was carried out on patients with HbA1c ranged at baseline from 8.4% to 8.5% and it showed decrease up to 1.1% with using Liraglutide and Glimepride [13].

Ar clinical study was carried out on Liraglutide as a 2nd line therapy with Metformin and it showed decrease in HbA1c values 0.7% with low dose (0.6 mg/day) and 1% for high dose (1.2 and 1.8 mg/day) [14].

A clinical study has been carried out on Liraglutide as a 3rd line therapy with Metformin and Rosiglitazone and it showed reduction in HbA1c by 1.5% for both daily doses of 1.2 and 1.8 mg/day [15].

Weight loss

Recently, Liraglutide has been used for weight loss and it showed promising results.

Five randomized, placebo-controlled trials of liraglutide for weight management were identified. In addition to recommended diet and physical activity, liraglutide consistently resulted in a 4 to 6 kg weight loss [16].

Cardiovascular and lipid profile

Use of liraglutide was associated with lowering the risk of MACE (major associated cardiovascular events) and death in patients with type2 DM & high cardiovascular risk using basal insulin [17].

It lowers systolic blood pressure and lipid profile [18].

Adverse effects

Unfortunately like many drug agents, Liraglutide has been linked to some adverse effects; The most common (prevalence greater than 5%) are nausea, hypoglycemia, diarrhea, constipation, headache, dyspepsia, fatigue, abdominal pain and increased level of Lipase enzyme [19]. A randomized study has been carried out on a population with type 2 DM at high CVS risk and it showed that acute pancreatitis occurred in 0.4% in patients treated with Liraglutide [20]. This can be assessed by increase in pancreatic enzymes level and Ultrasound in which the pancreas appears as a hypoechoic mass (Figure 2).

Figure 2

It is marked with a black box warning about the risk of medullary Thyroid Carcinoma as it has been shown to increase Thyroid C-cell tumors in rats and mice. However, a study has been carried out over 6000 patients and it showed no increased risk for MTC in humans [20].

Figure 3

Conclusion

The therapeutic promise of Liraglutide is now evident from clinical data. It showed the potential to achieve good glycemic control in type 2 DM, weight loss and improvement in Cardiovascular and lipid profile. However, challenges remain because of its high cost, the need for injection and other adverse effects.

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Volume 3 Issue 10 October 2019

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