

Lixisenatide: A New Glucagon-Like Peptide-1 Agonist

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During 2010, 8.3% of the United States populations were living with diabetes [1]. Over 80% of those diagnosed with diabetes are classified as being overweight [2]. Excessive weight increases the extent of insulin resistance, thus, in overweight individuals; weight loss should be a priority therapeutic target in the management of diabetes [3].

Currently available agents that are considered weight neutral or have the propensity to induce weight loss include biguanides, alpha-glucosidase inhibitors, Dipeptidyl-Peptidase IV (DPPIV) inhibitors, glucagon-like peptide 1 (GLP-1) receptor agonists, amylin analogs, and sodium-glucose cotransporter-2 inhibitors. Among these agents, metformin, GLP-1 agonists, amylin analogs, and SGLT-2 inhibitors are the most potent at inducing weight loss with metformin, exenatide, liraglutide, exenatide once weekly, pramlintide, and canagliflozin reducing body weight by 1.9 kg, 3.1 kg, 2.4 kg, 2.0 kg, 2.7 kg, and 3.4 kg, respectively [4-12].

Substantial development of GLP-1 agonists have revolved around extending the duration of action via peptide modifications through N-terminal amino acid substitutions, incorporation of microspheres to prolong drug release, and covalent and non-covalent binding to proteins and large molecules [13]. Currently, albiglutide, lixisenatide, and dulaglutide are among the GLP-1 agonists farthest along the pipeline in phase 3 trials, with lixisenatide leading in published phase 3 clinical trial data.

Lixisenatide, similar to exenatide, is a GLP-1 agonist based on exendin-4, which was isolated from the salivary glands of the Gila monster [13,14]. It carries seven amino acid substitutions at its N-terminal to protect against degradation by DPPIV prolonging its half-life to 3-4 hours. Although the relatively short half-life of lixisenatide calls for multiple daily dosing, the 0.6% difference in hemoglobin A1C reduction between once daily and twice daily dosing suggests it may be administered once daily [13].

Currently, the use of lixisenatide has been evaluated in multiple phase 3 clinical trials [15-23]. The earliest trial, Get Goal-Mono, was a 12-week, randomized, double-blind, placebo-controlled study evaluating lixisenatide as monotherapy in a one- (10 µg daily for 2 weeks and then 20 µg daily) and two-step (10 µg daily for 1 week, 15 µg daily for 1 week, and then 20 µg daily) dose titration with matching placebo. A total of 361 type 2 diabetic patients who were treatment naive were enrolled in the trial and the results indicate study patients significantly reduced their hemoglobin A1C by 0.66% and 0.54% compared to placebo in the one- and two-step groups, respectively. In addition, patients experienced a 2 kg weight loss regardless of treatment and Gastrointestinal (GI) side effects were the most common adverse events occurring in 32% of the treatment group. Rates of hypoglycemia were low in both treatment and placebo groups (1.7% versus 1.6%) [15].

In a similar trial evaluating 484 patients already on metformin in a 24-week analysis (Get Goal-F1), the data revealed nearly identical results as Get Goal-Mono with a 0.5% and 0.4% statistically significant reduction in hemoglobin A1C when compared to placebo. In this trial with patients already on metformin, weight reductions were limited to 1.0 and 1.1kg compared to placebo in the one- and two-step titration groups, respectively. The most common side effects were GI related

(nausea and vomiting) and occurred in 41.6% in the one-step titration group and 47.2% in the two-step titration group. Similar to the Get Goal-Mono trial, rates of hypoglycemia were low at 2.2% and 0.6% in the treatment and placebo groups, respectively [16].

Its head to head trial against exenatide (Get Goal-X) in 639 patients with type 2 diabetes on metformin was conducted in a 24-week, randomized, open-labeled design. The results revealed a non-inferior hemoglobin A1C reduction of 0.79% and 0.96% for lixisenatide and exenatide, respectively. The weight loss associated with exenatide was 3.98 kg compared to 2.96 kg for lixisenatide and GI side effects were also the most common adverse events in this trial with slightly more nausea in the exenatide group (35.1%) compared to the lixisenatide group (24.5%). Symptomatic hypoglycemia occurred in significantly less patients in the lixisenatide group (2.5% versus 7.9%) [17].

Two 24-week, randomized, double-blind, placebo-controlled trials evaluated the hemoglobin A1C lowering effect of lixisenatide with a background consisting of a sulfonylurea (Get Goal-S) or pioglitazone (Get Goal-P), both of which allowed metformin to be part of the study regimen [18,19]. The Get Goal-S trial randomized 859 patients to lixisenatide or placebo in a 2:1 ratio, which resulted in a statistically significant hemoglobin A1C reduction in the lixisenatide group (0.85% versus 0.1%, $p < 0.0001$). There was a statistically significant weight reduction of 1.76 kg in favor of lixisenatide, which is expected with GLP-1 agonists; however, patients in the placebo group who were on a sulfonylurea also lost weight at a rate of 0.93 kg over 24 weeks. The most common adverse events for lixisenatide and placebo included nausea (25.3% versus 7.0%) and vomiting (8.7% versus 3.5%). Symptomatic hypoglycemia occurred in 15.5% and 12.3% of participants in the lixisenatide and placebo groups, respectively [18]. Rates of hypoglycemia were not statistically significant [18] and the greater rates documented in this trial may be due to the background therapy consisting of a sulfonylurea. The Get Goal-P trial was almost half the size of Get Goal-S with 484 patients randomized to lixisenatide or placebo in a 2:1 ratio. Their findings revealed a statistically significant hemoglobin A1C reduction of 0.9% in the lixisenatide group compared to 0.34% in the placebo group, which were similar to the data presented in the Get Goal-S trial. In contrast to the Get Goal-S study, participants in the treatment group lost only 0.2 kg over 24 weeks and participants in the placebo group gained 0.2 kg. The authors suggested pioglitazone was likely responsible for the less robust weight loss in the treatment

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group. Consistent with the trials summarized above, GI side effects remain a large contributor of adverse events with 36.5% versus 28.6% in the lixisenatide and placebo groups, respectively. Rates of symptomatic hypoglycemia were limited, compared to the Get Goal-S trial, at 3.4% in the lixisenatide group and 1.2% in the placebo group.

A total of three randomized, double-blind, placebo-controlled trials, Get Goal-L [20], Get Goal-L-Asia [21], and Get Goal-Duo-1 [22], studied the use of lixisenatide in the setting of background basal insulin therapy with or without oral agents over the course of 24 weeks [20-22]. The Get Goal-L study randomized 496 participants in a 2:1 ratio to lixisenatide or placebo with or without the addition of metformin to the background of basal insulin therapy. Hemoglobin A1C reductions were greater in the lixisenatide group compared to placebo (0.7% versus 0.4%, $p=0.0002$). A statistically significant weight reduction of 1.8kg in the treatment group compared to the 0.5kg in the placebo group was observed and the most common adverse reactions reported with lixisenatide include nausea and vomiting. Rates of symptomatic hypoglycemic episodes in this trial reached 26.5% with lixisenatide and 21.0% with placebo [20]. In the Get Goal-L-Asia trial, 311 participants recruited from four countries in Asia were randomized to lixisenatide or placebo in a 1:1 ratio. All participants were on a background therapy of basal insulin with or without a sulfonyl urea.

The findings revealed a significant hemoglobin A1C reduction of 0.77% in the lixisenatide group compared to a 0.11% hemoglobin A1C elevation in the placebo group ($p<0.0001$). A small weight reduction of 0.38 kg and a negligible weight gain of 0.06 kg were observed in the lixisenatide and placebo group, respectively; however, when compared between treatment groups, no statistically significant difference was detected. The most common adverse events for lixisenatide were GI in nature and consisted mainly of nausea and vomiting. Symptomatic hypoglycemia topped all the other Get Goal trials at 42.9% for lixisenatide and 23.6% for placebo. According to the authors, the incidence of hypoglycemia was greater when participants were on lixisenatide, insulin, and a sulfonylurea compared to lixisenatide and insulin alone, which approached rates similar to the placebo group [21]. The Get Goal-Duo-1 trial evaluated 446 participants randomized to lixisenatide or placebo with a background therapy of insulin glargine and metformin with or without a sulfonylurea, glinide, or thiazolidinedione. A statistically significant difference in hemoglobin A1C was observed in the lixisenatide group compared to placebo (0.7% versus 0.4%, $p<0.0001$). Increases in weight were documented in both the lixisenatide and placebo groups (0.3 kg versus 1.2kg), however the difference remained statistically significant ($P=0.0012$). The adverse events were dominated by GI side effects and symptomatic hypoglycemia occurred in 20.2% of the lixisenatide group and 11.7% of the placebo group [22].

Get Goal-M was a 24-week, double-blind and placebo-controlled trial that randomized 680 patients on metformin to either morning or evening injections of lixisenatide with matching placebo in a 3:1 ratio (lixisenatide: placebo). The findings revealed a nearly identical hemoglobin A1C reduction of 0.9% for the morning injection compared to a 0.8% reduction for the evening injection. Weight reductions also remained identical with a 2kg reduction in both active treatment groups. Nausea and vomiting were the most frequent side effects in the lixisenatide arm. More symptomatic hypoglycemic events were observed in the evening injection group (5.1%) when compared to the morning injection group (2.4%) and hypoglycemia generally occurred within hours of dose administration. Although the evening lixisenatide injections displayed a numerically greater number of hypoglycemic episodes, the absolute rates of hypoglycemia were low [23].

It is clear that lixisenatide has been extensively studied in multiple phase-3 clinical trials simulating patients with diabetes regimens that we treat in our clinical practices. In addition, Sanofi has initiated their ongoing cardiovascular study named ELIXA and has already collected early interim results [24]. Unfortunately, as of September 2013, Sanofi has withdrawn its New Drug Application for lixisenatide with concerns that public disclosure of their interim cardiovascular data could jeopardize the integrity of the ELIXA trial. Sanofi plans on resubmitting their application to the U.S. Food and Drug Administration after the disclosure of the full results following the completion of the ELIXA study [25].

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