Review Article

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Lixisenatide in the Treatment of Diabetes

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Abstract

Diabetes and its complications continue to have a major impact on the morbidity and mortality in both the developed and developing world. While the condition does have a gamut of options at the physician's disposal such as insulin, metformin, GLP analogues, DPP-4 inhibitors and SGLT-2 inhibitors, each of these drugs are not without its own set of unique nuances. A significant proportion of patients do not achieve adequate glucose control.Lixisenatide is a novel GLP-1 agonist that is approved for the treatment of diabetes. The drug is given at a dose of 10 mcg once daily for 14 days via subcutaneous route using a pre-filled pen. Gastrointestinal intolerance is a common issue as seen with other GLP agonists. Efficacy with the drug has been modest and been shown to be non-inferior to other GLP agonists such as exenatide. The once daily dosing, low risk of hypoglycemia and the relative cost benefit may make it an attractive option for physicians to prescribe this molecule in patients with uncontrolled diabetes.

Keywords: Diabetes; Lixisenatide; GLP-1 Agonist; Subcutaneous; GET GOAL**.**

Introduction

Diabetes mellitus is a widespread non-communicable disease that affects epidemic proportions. It is estimated that 377 million people suffer diabetes and this number can extend to 552 million by 2025 [1-3]. Complications of diabetes include diabetic ketoacidosis, hyper-osmolar non-ketotic coma, diabetic retinopathy, diabetic peripheral neuropathy, diabetic foot, cardiovascular complications, peripheral arterial disease and hypertension. Contemporary medications are unable to pre-empt the long-term consequences of diabetes. A new era of treatment paradigm came out based on incretin hormone that is GLP-1 in 2005 following the approval of exenatide injection in patients not responding to standard therapy [4]. Subsequent to this, several other GLP -1 agonists have entered the market which includes drugs such as liraglutide, albiglutide and dulaglutide [5]. Lixisenatide is the most recent drug approved by FDA for diabetes and we have attempted to summarize the mechanism of action, efficacy, safety and current status of this novel molecule.

Mechanism of Action

Lixisenatide is a glucagon like peptide 1 receptor agonist. It binds to the GLP-1 receptor and potentiates insulin release from the pancreatic beta cells in the setting of hyperglycemia especially after a meal. This action is brought about by the increase in the cAMP. It delays gastric emptying and thus post prandial glucose elevations are reduced. The drug also has a suppressive action on glucagon secretion [6].

Efficacy

Lixisenatidein combination with oral therapy was tested in several randomized controlled trials [7-12]. While the GET GOAL-Asia was limited to the Asian

population, the rest of the studies included patients of all races including Black, Caucasian, Asian and others. Except the Get Goal Mono which evaluated monotherapy with lixisenatide, all other trials evaluated patients who were on concomitant drug therapy with existing oral hypoglycemic agents and/ or insulin. Lixisenatide was found to be uniformly superior to placebo with respect to the reduction of HbA1c following 24 weeks of therapy in all trials. The Get Goel M study also showed that timing of the lixisenatide dosage as to whether it was given in the morning or evening hardly made any difference to the efficacy of the molecule.There was also a dose dependent response relationship with the 20-mcg dose showing the best efficacy to tolerability ratio. The drug is also found to be non-inferior to exenatide twice daily in its reduction of HbA1c [13]. Lixisenatide also showed significant reduction in fasting and post prandial blood glucose levels.

Safety

The most common safety concerns for lixisenatide as seen in clinical trials were gastro intestinalwhich includes nausea, vomiting and diarrhea. The gastrointestinal discomfort was disconcerting enough to cause almost 7% of patients to withdraw from the study in comparison to a 3% withdrawal rate in placebo. A rare severe adverse reaction that can be potentially life threatening is pancreatitis which is a well-known adverse event with GLP-1 analogues. Hypoglycemia was also commonly observed and those patients who were on concomitant therapy with insulin or sulfonylureas were at a greater likelihood of experiencing these adverse effects [7-12].

Pharmacokinetics

Lixisenatide is given at a starting dosage of 10 mcg once daily for 14 days via subcutaneous route using a pre-filled pen. It is followed by a dose of 20 mcg once daily from day 15 onwards. The drug reaches maximal concentration in 1-3.5 hrs. The volume of distribution is 100 liters and the half-life is 3 hours [14].

Current Status

Lixisenatide was approved by the European Medical Agency in 2013 [15]. Due to the controversy associated with rosiglitazone with respect to its cardiovascular safety, FDA mandated that the sponsor to complete phase 3 trials to look at the cardiovascular safety of the molecule which resulted in relatively delayed approval in the American market in 2016 [16]. One advantage about this drug compared to exenatide is the once daily dosage it requires.The cost advantage of lixisenatide over other GLP analogues could be a significant factor in influencing which of these drugs to prescribe. Nevertheless, the drug has not been shown to have greater efficacy over other GLP analogues and head to head trials with these agents are still lacking. Some authors have even surmised lixisenatide to be a "me-too GLP analogue" on account of its run-of-the-mill performance in clinical trials.

Table 1: Summary of phase 3 clinical trials of lixisenatide

Author	Trial name	Population	Sample size	Groups	Primary end point	Result
Riddle MC et al (2015)	Get Goal -Duo 1	T2DM for atleast 1 year with HbA1c ≥7.0 and ≤10% with concomitant OHA	446	1) Lixisenatide 2) Placebo	absolute change of HbA1c from baseline to week 24	HbA1c decrease from baseline was significantly greater with lixisenatide compared with placebo;
Fonseca VA et al	Get Goal-Mono	T2DM not currently receiving glucose-lowering therapy and with glycated hemoglobin (HbA1c) ≥7.0% and ≤10.0%.	361	1)lixisenatide 2-step dose increase (10 mg for 1 week, 15 mg for 1 week, and then 20 mg), 2)lixisenatide 1-step dose increase (10 mg for 2 weeks and then 20 mg), 3) placebo 2-step dose increase, and 4) placebo 1-step dose increase.	change in HbA1c from randomization to week 24	Both one step and two step regimens provided better HbA1c reduction than placebo. No difference between one and two step regimen.
Riddle MC et al	Get Goal- L	T2 DM on basal insulin dose of ≥ 30 units/d and HbA_{1c} of 7-10%	495	1)Placebo 2) Lixisenatide	change in HbA1c from randomization to week 24	Lixisenatide showed better reduction of HbA1c compared to placebo.
Seino Y etal	Get Goal- L Asia	T2DM on stable insulin therapy with or without sulfonylurea	311	1)Lixisenatide 2)Placebo	Change in HbA_{1c} from baseline to week 24	Lixisenatide had a more significant reduction in HbA_{1c}
Ahren B etal	Get Goal- M	T2DM with inadequate control with metformin for at least 3 months	680	1)Lixisenatide morning 2)Placebo morning 3)Lixisenatide evening 4)Placebo evening	Absolute change in HbA1c from baseline to week 24	No difference in HbA1c reduction between the morning and evening dose of lixisenatide.

Conclusion

Lixisenatide is a once daily GLP analogue that has been recently approved by the US FDA. The drug has shown modest results in clinical trials with its efficacy that is comparable to the existing GLP analogues. In terms of safety, the drug is marginally better with lesser incidence of gastrointestinal intolerance compared to the other GLP analogues. As the drug gives patients the advantage of requiring lesser dose of insulin, it may be considered as one of the options in the management of diabetic subjects who do not respond to the first line therapy with metformin/sulfonylureas.

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