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Review Article

Lixisenatide, a Novel GLP-1 Receptor Agonist, for the Treatment of Type 2 Diabetes

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ABSTRACT

Diabetes mellitus (DM) is an important global public health problem. Despite availability of many antidiabetic drugs, the glycemic goals cannot be achieved and serious complications of diabetes continue to happen. The adverse effects associated with antidiabetic medications are another issue. Glucagon like peptide-1 (GLP-1) receptor agonists are novel class of drugs, used for the treatment of type 2 DM. Recently lixisenatide is approved by United States Food and Drug Administration (US FDA) for the treatment of type 2 diabetes as add-on drug. Lixisenatide exerts its actions by acting on GLP-1 receptors, resulting in increase in insulin secretion, decrease in glucagon release, delay in gastric emptying and induction of satiety. Lixisenatide has demonstrated its clinical efficacy as antidiabetic by lowering of glycated hemoglobin (HbA_{1C}) levels and reduction in 2 h postprandial plasma glucose (PPG) levels when used alone. Lixisenatide also has exerted synergistic antidiabetic effects when administered with metformin, sulfonylureas, pioglitazone and basal insulin in terms of greater fall in HbA_{1C} levels and better control of 2 h PPG. Lixisenatide has been found to be non-inferior to other GLP-1 receptor agonists in reducing HbA_{1C} and 2 h PPG with favourable side effect profile. The lixisenatide is less costly and has lower incidence of hypoglycaemia compared to exenatide and liraglutide. Overall it may serve as good add-on treatment to the existing antidiabetic drugs.

Keywords: Lixisenatide, GLP-1, Type 2 diabetes, Antidiabetic

INTRODUCTION

Diabetes mellitus (DM) is a chronic disease caused by a relative deficiency or ineffectiveness of plasma insulin. Diabetes is an important public health problem. In recent times, the prevalence of diabetes has been increasing steadily. In adult population, the global prevalence (age-standardized) of diabetes has nearly doubled since 1980, which has increased from 4.7% to 8.5%. [(1)] The global prevalence of diabetes is predicted to rise from 366 million in 2011 to 522 million in 2030 and India itself will have 79.4 million diabetics by 2030. [(2,3)]

Sulfonylureas (SUs), meglitinide analogues, dipeptidyl peptidase-4 (DPP-4) inhibitors, glucagon-like peptide-1 (GLP-1) receptor agonists (GLP-1 RAs), metformin, pioglitazone, α-glucosidase inhibitors, amylin analogues, bromocriptine, sodium-glucose cotransporter-2 (SGLT-2) inhibitors are the currently available drugs for the treatment of DM. Despite a large number of anti-diabetic agents available, serious complications of diabetes continue unabated and the desired glycemic goals are not achieved in many patients. Hence, there is a need for newer antidiabetic agents with better efficacy and safety profile. Lixisenatide is a novel GLP-1 RA, approved by US FDA in July 2016 for the treatment of type 2 DM. Currently two GLP-1 RAs exist in the clinical practice namely; exenatide and liraglutide, however, exenatide is required to be administered

twice daily subcutaneously, whereas liraglutide, which is administered once daily subcutaneously, is frequently associated with hypoglycemic episodes and is more costly compared to lixisenatide.

CHEMISTRY

Lixisenatide is a peptide containing 44 amino acids, which is amidated at the C-terminal amino acid (position 44) and has molecular weight of 4858.5 and molecular formula as $C_{215}H_{347}N_{61}O_{65}S$. [4]

MECHANISM OF ACTION

On ingestion of food containing fat, protein and/or glucose, GLP-1 is secreted by enteroendocrine L cells of the gut and is released into the blood stream. GLP-1 acts on GLP-1 receptor (GLP-1R) which is G protein coupled receptor and results in stimulation of insulin secretion, decrease in glucagon secretion, delay in gastric emptying and induction of satiety through cyclic adenylyl monophosphate (cAMP) pathway. [5] Endogenous GLP-1 is metabolized and inactivated by the enzyme DPP-4. [6] Lixisenatide like other synthetic GLP-1 RAs is resistant to the action of DPP-4. Besides acting as endogenous GLP-1, synthetic GLP-1 RAs are also known to have anti-apoptotic effects on β cells, induce β-cell proliferation and insulin biosynthesis. [4,7]

PHARMACOKINETICS

Lixisenatide is administered subcutaneously (sc), 1 h prior to the major meal of the day once daily. On sc administration, it is absorbed rapidly and has median Tmax of 1–3.5 h. Lixisenatide is only moderately bound to human proteins (55%) and the apparent volume of distribution (V_z/F) after sc administration is 100 L. The drug is eliminated in urine, probably after proteolytic degradation as small and inactive peptides with an elimination half life of ~3 h. [8]

CLINICAL TRIALS DATA

Table 1. Clinical trial data summary of lixisenatide

Trial	Duration in weeks (Number of participants)	Background treatment	Study drugs	HbA_{1C} (%) Change from baseline	2 h PPG (mmol/L) Change from baseline	Adverse effects
GetGoal-Mono [9]	12 weeks (361)	None	lixisenatide 2-step	-0.73***	-5.47***	Nausea (24.2%), headache (8.3%), vomiting & dizziness (7.5%), nasopharyngitis (5%), hypoglycaemia (2.5%)
			lixisenatide 1-step	-0.85***	-4.51***	Nausea (20.2%), headache (7.6%), vomiting (6.7%), dizziness (3.4%), nasopharyngitis (4.2%), hypoglycaemia (0.8%)
			placebo	-0.19	-0.65	Nausea (4.1%), headache (11.5%), vomiting (6.7%), dizziness (2.5%), nasopharyngitis (3.3%), hypoglycaemia (1.6%)
Lixisenatide vs liraglutide [10]	28 days (148)	None	lixisenatide	-0.3	-3.91***	Dyspepsia (7.8%), diarrhoea (2.6%), abdominal distension (6.5%)
			liraglutide	-0.5	-1.38	Dyspepsia (16.9%), diarrhoea (15.5%), abdominal distension (12.7%)
GetGoal-M [11]	24 weeks (680)	Metformin	lixisenatide	-0.9***	-5.9***	Nausea (22.7%), vomiting (9.4%), hypoglycaemia (2.4%)
			lixisenatide	-0.8***	NR	Nausea (21.2%), vomiting (13.3%), hypoglycaemia (5.1%)
			placebo	-0.4	-1.4	Nausea (7.6%), vomiting (2.9%), hypoglycaemia (0.6%)
GetGoal-X [12]	24 weeks (634)	Metformin	lixisenatide	-0.79	NR	Nausea (24.5%), hypoglycaemia (2.5%)
			exenatide	-0.96	NR	Nausea (35.1%), hypoglycaemia (7.9%)
Lixisenatide vs sitagliptin [13]	24 weeks (319)	Metformin	lixisenatide	-0.7	-3.4***	Hypoglycaemia (0.6%)
			sitagliptin	-0.7	-1.4	Hypoglycaemia (1.9%)

Table 1: To be continued…						
GetGoal-M Asia [14]	24 weeks (391)	Metformin ± SUs	Lixisenatide	-0.83**	-5.61***	Nausea (16.3%), vomiting (7.7%), hypoglycaemia (5.6%), dizziness (8.7%)
			Placebo	-0.47	-1.33	Nausea (2.6%), vomiting (1%), hypoglycaemia (2.6%), dizziness (4.1%)
GetGoal-S [15]	24 weeks (859)	SUs± metformin	lixisenatide	-0.85***	-6.19***	Discontinuation (9.8%), nausea (25.3%), vomiting (8.7%)
			placebo	-0.1	-0.21	Discontinuation (4.9%), nausea (7%), vomiting (3.7%)
PDY6797 [16]	6 weeks (120)	SUs ± metformin.	lixisenatide	-0.94***	-150.2***	Nausea (41%), diarrhoea (7.7%), hypoglycaemia (20.5%)
			lixisenatide	-1.13***	-128.7***	Nausea (19.5%), diarrhoea (22%), hypoglycaemia (22%)
			placebo	-0.41	-25.3	Nausea (2.5%), diarrhoea (12.5%), hypoglycaemia (7.5%)
GetGoal-P [17]	24 weeks (484)	Pioglitazone± metformin	lixisenatide	-1.0***	NR	Nausea (23.5%), vomiting (6.8%), hypoglycaemia (3.4%)
			placebo	-0.5	NR	Nausea (10.6%), vomiting (3.6%), hypoglycaemia (1.2%)
GetGoal-L [18]	24 weeks (495)	Basal insulin ± metformin	lixisenatide	-0.7**	-5.5***	Hypoglycaemia (26.5%)
			placebo	-0.4	-1.7	Hypoglycaemia (21%)
GetGoal-Duo 2 [19]	26 weeks (894)	Basal insulin ± metformin	lixisenatide	-0.6	-3.64	Discontinuation (5%), nausea (25.2%), vomiting (8.7%), lipase (0.7%), hypoglycaemia (35.9%)
			insulin glulisine once daily	-0.6	-1.57	Discontinuation (0.7%), nausea (1.7%), vomiting (1.7%), lipase (0.3%), hypoglycaemia (46.5%)
			insulin glulisine three times a day	-0.8	-1.41	Discontinuation (1%), nausea (1%), vomiting (2%), lipase (1%), hypoglycaemia (52.4%)
Lixisenatide vs liraglutide [20]	8 weeks (142)	Insulin glargine ± metformin	lixisenatide	-0.6	Reduction from 15.7±6.7 to 3.5 ± 6.5 h·mmol/L**	Lipase (2.1%), hypoglycaemia (29.2%)
			liraglutide	-0.7	Reduction from 15.6± 5.6 to 9.5 ± 5.3 h·mmol/L	Increase in heart rate, diastolic BP, lipase (4.3%), hypoglycaemia (19.1%)
			liraglutide	-0.7*	Reduction from 17.0± 5.7 to 8.7 ± 3.5 h·mmol/L	Increase in heart rate, diastolic BP, lipase (2.1%), hypoglycaemia (21.3%)
GetGoal-Duo 1 [21]	24 weeks (446)	Basal insulin ± metformin ± thiazolidinedione	lixisenatide	-0.7***	-3.1***	Hypoglycaemia (20.2%), serious AE (7.6%), injection site reactions (6.7%)
			placebo	-0.4	0.1	Hypoglycaemia (11.7%), serious AE (4.5%), injection site reactions (2.2%)
GetGoal-L Asia [22,23]	24 weeks (311)	Basal insulin ± SUs	lixisenatide	-0.77***	-7.96***	Discontinuation (9.1%), GI (61%), nausea (39.6%), headache (10.4%), hypoglycaemia (42.9%)
			placebo	+0.11	-0.14	Discontinuation (3.2%), GI (14.6%), nausea (4.5%), headache (1.9%), hypoglycaemia (23.6%)
GetGoal-O [24]	24 weeks (350)	Basal insulin/SUs/other	lixisenatide	-0.57***	-5.12***	Hypoglycaemia (17.6%), nausea & vomiting (26.1%), discontinuation (4.5%)
			placebo	0.06	-0.07	Hypoglycaemia (10.3%), nausea & vomiting (7.5%), discontinuation (0.6%)

(*: P<0.01, **: P<0.001, ***: P<0.0001, HbA_{1C}: glycated haemoglobin, PPG: Post-prandial plasma glucose, SU: Sulfonylurea, NR: not reported)

Lixisenatide has demonstrated its clinical efficacy as antidiabetic by lowering of glycated haemoglobin (HbA_{1C}) levels and reduction in 2 h postprandial plasma glucose (PPG) levels when used alone. Its antidiabetic effects have been synergistic when administered with metformin, SUs, pioglitazone and basal insulin in terms of greater fall in HbA_{1C} levels and better control of 2-h PPG. (Table 1)

Lixisenatide though has not demonstrated significant difference in HbA_{1C} levels as compared to exenatide but its use has been associated with fewer episodes of nausea and hypoglycaemia as compared to exenatide. (Table 1)

The studies comparing lixisenatide with liraglutide showed that, lixisenatide produced significantly higher reduction in 2 h PPG as compared to liraglutide, while the effects on HbA_{1C} levels were non-inferior. Use of lixisenatide has been observed to be associated with less occurrences of adverse effects like dyspepsia, abdominal distension, diarrhoea and hypoglycaemia compared to liraglutide. (Table 1)

ADVERSE EFFECTS

The most common adverse reactions observed in patients treated with lixisenatide are nausea, vomiting, headache, diarrhea, dizziness, and hypoglycaemia. Other less frequently observed reactions are injection site reactions (e.g., pain, pruritus and erythema), dyspepsia, constipation, abdominal distension and pain and allergic reactions (anaphylactic reaction, angioedema and urticaria). (Table 1)

PRECAUTIONS

Patients with history of anaphylaxis with other GLP-1 RAs should be monitored closely for allergic reactions to lixisenatide.

Patient should be watched for the signs of hypoglycaemia although the risk is lower than other parenteral antidiabetic agents.

Lixisenatide is not recommended in patients with end-stage renal disease. [(25)]

USE IN SPECIAL POPULATION

Renal disease

Mild renal impairment does not influence pharmacokinetics or tolerability of lixisenatide. Therefore, no dose adjustment is required for patients with glomerular filtration rate (GFR) 50–80 mL/min. Conversely, in subjects with moderate (GFR 30–50 mL/min) and severe (GFR 15–30 mL/min) renal impairment the AUC is increased by 24 and 46% respectively and need dose reduction. [(8)]

Liver disease

There are no published studies evaluating the pharmacokinetics of lixisenatide in patients with hepatic impairment. Hepatic dysfunction is not expected to affect the pharmacokinetics of lixisenatide, and dose adjustment in patients with hepatic impairment is not recommended.

DRUG INTERACTIONS

Lixisenatide delays gastric emptying which may impact absorption of concomitantly administered oral medications. Oral medications that are particularly dependent on threshold concentrations for efficacy, such as antibiotics, or medications for which a delay in effect is undesirable, such as acetaminophen, should be administered 1 h before lixisenatide. Oral contraceptives should be taken at least 1 h before lixisenatide administration or 11 h after the dose of lixisenatide.

APPROVED INDICATIONS AND DOSE

Lixisenatide has been approved by US FDA as an adjunct to diet and exercise to improve glycemic control in adults with type 2 DM. The starting recommended dose of lixisenatide is 10 µg once daily sc (at abdomen, thigh or upper arm) for 14 days and from day 15, dosage can be increased to 20 µg once daily. [(4)]

In India, lixisenatide is available as a pre-filled pen of either 10 mcg or 20 mcg and in fixed dose combination with insulin glargine.

LIMITATION OF LIXISENATIDE

Though cost of lixisenatide is relatively higher than other antidiabetic drugs but it is lower than liraglutide or exenatide. A pharmacoeconomic analysis in England showed that the actual cost per item dispensed in primary care is lowest for lixisenatide (£60.28) than exenatide (£82.35) or liraglutide (£100.98). [(26)]

CONCLUSIONS

Lixisenatide is a novel and effective GLP-1 RA for the treatment of type 2 DM patients. Lixisenatide can be used in clinical

practice in combination with basal insulin as well as with other antidiabetic drugs like metformin, sulfonylureas, pioglitazone and carries low risk of hypoglycaemia.

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