Liraglutide: First Once-Daily Human GLP-1 Analogue

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ABSTRACT

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The gastrointestinal hormones glucose- dependent insulinotropic polypeptide (GIP) and glucagon-like peptide-1 (GLP-1), termed incretins, are essential regulators of normal glucose homeostasis. The drug substance, Liraglutide, is a long acting analogue of the naturally occurring human GLP-1 (7-37) with 97% homology and a lipophilic substituent for prolongation of half life.

Liraglutide is available in a pre-filled, multi-dose pen-injector containing 6.0 mg/ml of the drug substance in solution presented for subcutaneous injection.

Liraglutide provided significantly better glycemic control than Rosglitazone or insulin glargine in combination trials. Liraglutide improved pancreatic beta-cell function, consistently led to weight loss, and was associated with a low risk of hypoglycaemia. Liraglutide was generally well tolerated, with the most common adverse events being gastrointestinal events, such as nausea, which decreased over time.

Keywords: GLP 1 Analogue, Liraglutide, Incretin, Hypoglycemia, Weight loss.

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Current status of type 2 diabetes in India and unmet needs

As per the latest International Diabetes Federation (IDF) released in 2009, India tops the list of countries with highest number of people with diabetes. In India there are close to 51 million people with diabetes (IDF, 2009). The situation is expected to get worse in the forthcoming years with close to 87 million suffering from type 2 diabetes by 2025. Even in rural areas prevalence of diabetes is rising rapidly. Ageing of the population and increase in obesity are the main causes of this "diabetes epidemic". Obesity, mainly when fat is distributed predominantly at the abdominal obesity is the main risk factor for type 2 diabetes. In India as in all over the world, the diabetes epidemic is due to the increase in prevalence of obesity, linked to "westernized" lifestyle, namely changes in nutritional habits, with increased intake of saturated fats, refined sugars and alcohol, and reduced intake of fibres, and at the same time, reduction in physical activity (Wild S et al, 2004).

In addition to the core pathophysiologic defects in type 2 diabetes insulin resistance and β- cell failure, impaired incretin pathway and unsuppressed glucagon secretion are now recognised to be the other important etiologic components in type 2 diabetes (Unger J et al, 2010). As per Defronzo's ominous octet in addition to the muscle, liver, and β -cell, the fat cell (accelerated lipolysis), gastrointestinal tract (incretin deficiency/ resistance), β-cell (hyperglucagonemia), kidney (increased glucose reabsorption), and brain (insulin resistance) all play important roles in the development of glucose intolerance in type 2 diabetic individuals (Defronzo RA, 2009). To address these multiple pathophysiologic defects combination of drugs required or drugs should have multiple effects to address these issues.

Incretin concept

Insulin response following oral glucose is more than intravenous glucose. This interesting observation is termed as "incretin effect" (Creutzfeldt W et al,1983). Nutrient intake stimulates the secretion of the gastrointestinal incretin hormones, glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP), which exert glucose-dependent insulinotropic effects and assist pancreatic insulin and glucagon in maintaining glucose homeostasis. GLP-1 also suppresses glucose- dependent glucagon secretion, slows gastric emptying, increases satiety, and reduces food intake (Nauck M et al, 2009). The incretin effect, mediates approximately 50-70% of the overall insulin responses after a mixed meal or glucose ingestion in healthy subjects.

The gastrointestinal hormones glucose- dependent insulinotropic polypeptide (GIP) and glucagon-like

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peptide-1 (GLP-1), termed incretins, are essential regulators of normal glucose homeostasis. It has been shown that "incretin effect" is impaired in type 2 diabetes (Nauck M, 1986), characterized by decreased responsiveness to GIP and markedly reduced GLP-1 concentration. It has been speculated that a reduced incretin effect might precede the onset of hyperglycaemia in patients with type 2 diabetes.

Incretin therapy

The administration of GLP-1 improves glycemic control, but GLP-1 is rapidly degraded by the enzyme dipeptidyl peptidase-4 (DPP-4) (Nauck M, 2009). Hence to use GLP-1 therapeutically two types drugs have been developed. DPP-4 inhibitors, like Sitagliptin, Vildagliptin and Saxaglipitin, also known as incretin enhancers inhibit DPP-4 enzyme and thereby raise the concentration of endogenous GLP-1 and GIP. GLP-1 agonists, like Exenatide and Liraglutide, also known as incretinmimetics are resistant DPP-4 action and act like native GLP-1 via GLP-1 receptors. Liraglutide is the first once daily human GLP-1 analogue currently approved for marketing across the globe.

Liraglutide: Bench to bedside

The drug substance, Liraglutide, is a long acting analogue of the naturally occurring human GLP-1 (7-37) with 97% homology and a lipophilic substituent for prolongation of half life. The analogue is produced as the polypeptide precursor by r-DNA technology with Saccharomyces cerevisiae (Summary of product characteristics, Victoza®, 2009). Liraglutide is a GLP-1 analogue in which lysine at position 34 has been replaced with arginine, and palmitic acid has been attached via glutamoyl spacer to lysine at position 26. Liraglutide has a half- life close to 13 hrs making it suitable for once daily administration. Following subcutaneous administration, the protracted action profile is based on three mechanisms: self-association, which results in slow absorption, binding to albumin and stability towards the DPP-4 enzyme both results in a prolonged plasma half-life. Liraglutide is available in a pre-filled, multi-dose pen-injector containing 6.0 mg/ml of the drug substance in solution presented for subcutaneous injection.

To evaluate the clinical benefits of Liraglutide a comprehensive clinical development program entitled Liraglutide Effect and Action in Diabetes (LEAD) has been conducted. LEAD 1-6 studies evaluated the potential benefit of Liraglutide throughout the continuum of care in type 2 diabetes (Neumiller JJ et al, 2009).

Table 1. Comparison of Properties of GLP-1 agonists and DPP-4 inhibitors

Properties / effect	GLP-1 agonists	DPP-4 inhibitors
Mechanism of stimulation of insulin secretion exclusively through GLP-1 effect	Yes	Not clear
Restitution of insulin secretion (2 phases)	Yes	Yes
Glycemic control	Better	Good
Hypoglycaemia	No	No
Glucagon suppression	Yes	Minimal
Maintained counter-regulation by glucagon in hypoglycaemia	Yes	Not tested
Inhibition of gastric emptying	Yes	Marginal
Effect on body weight	Weight loss	Weight neutral
Side effects	Nausea	None observed
Administration	Subcutaneous	Oral

In LEAD studies, once-daily subcutaneous Liraglutide improved glycemic control compared with placebo or active comparator in adult patients with type 2 diabetes, both as monotherapy and in combination with one or two oral antidiabetic drugs such as metformin, sulphonylureas or Thiazolidinediones. Liraglutide provided significantly better glycemic control than Rosglitazone or insulin glargine in combination trials. Liraglutide improved pancreatic beta-cell function, consistently led to weight loss, and was associated with a low risk of hypoglycaemia. Liraglutide was generally well tolerated, with the most common adverse events being gastrointestinal events, such as nausea, which decreased over time. Efficacy of Liraglutide has been summarized in table 2 respectively (Neumiller JJ et al, 2009).

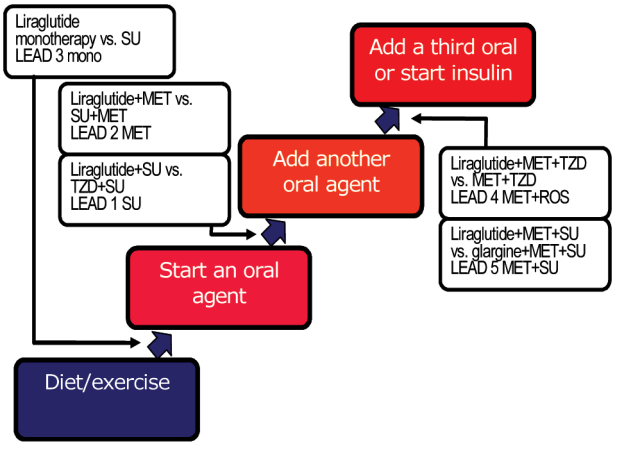

Figure 1. **Treatment Algorithm using Liraglutide**

Table 2. Efficacy Data of Liraglutide as Observed in LEAD Studies

Treatment arm	N (randomized)	Mean HbA1c Change from baseline (%)	Reaching ADA target <7.0%	Reaching IDF target <6.5	Mean FPG Change from Baseline (mmol/L)	Mean weight change from baseline (Kg)	Mean SBP Change from baseline (mmHg)
LEAD-3: Liraglutide as monotherapy versus glimepiride (Garber A et al, 2009)							
Liraglutide 1.2 mg	251	-0.8	43%	28%	-0.84	-2.05	-2.12
Liraglutide 1.8 mg	247	-1.1	51%	38%	1.42	2.45	3.64
Glimepiride 8 mg	248	-0.5	28%	16%	0.29	1.12	0.69
Liraglutide 1.8 mg Previously drug-naive	87	-1.6	62%	49%	-2.33	-1.61	-4.73
LEAD-2: Liraglutide added on to metformin versus glimepiride (Nauck M et al, 2009)							
Liraglutide 1.2 mg	241	-1.0	35%	20%	-1.64	-2.6	-2.8
Liraglutide 1.8 mg	242	-1.0	42%	24%	1.69	-2.8	2.3
Glimepiride 4 mg	244	-1.0	36%	22%	1.31	1.0	0.4
Placebo	122	0.1	11%	4%	0.40	-1.5	-1.8
Liraglutide 1.8 mg Previously drug-naive	83	-1.30	66%	39%	-1.36	-2.1	-1.18
LEAD-1: Liraglutide added on to glimepiride versus Rosglitazone (Marre M et al, 2009)							
Liraglutide 1.2 mg	228	-1.1	34%	21%	-1.57	0.3	-2.6
Liraglutide 1.8 mg	234	-1.1	42%	21%	1.59	-0.2	2.8
Rosiglitazone 4 mg	232	-0.4	21%	9.5%	0.88	2.1	0.9
Placebo	114	0.2	8%	4%	1.01	-0.1	2.3
Liraglutide 1.8 mg on previous OAD monotherapy	63	-1.38	56%	32.2%	-0.71	-0.11	-3.49
LEAD-4: Liraglutide added on to metformin + rosiglitazone versus placebo (Zinman B et al, 2009)							
Liraglutide 1.2 mg	178	-1.5	58%	37%	-2.20	-1.0	-6.7
Liraglutide 1.8 mg	178	-1.5	54%	36%	-2.40	-2.0	-5.6
Placebo	177	-0.5	28%	14%	-0.43	0.6	-1.1
LEAD-5: Liraglutide added on to metformin + glimepiride versus insulin glargine (Russel-Jones D et al, 2009)							
Liraglutide 1.8 mg	232	-1.3	53%	37%	-1.55	-1.81	-4.0
Insulin glargine	234	-1.1	46%	24%	-1.79	1.62	0.5
Placebo	115	-0.2	16%	11%	0.53	-0.42	-1.4
LEAD-6: Liraglutide added on to metformin and/or glimepiride versus exenatide (Buse JB et al, 2009)							
Liraglutide 1.8 mg	233	-1.1	54%	35%	-1.61	-3.24	-2.51
Exenatide 10 µg BID	231	-0.8	43%	21%	-0.60	-2.87	-2.0

Liraglutide vs. other incretin based therapies

Exenatide [exendin 4], a synthetic exendin 4 analogue was the first a glucagon-like peptide-1 (GLP-1) agonist to enter the market. Both exendin4 and its analogue, exendin 3, are 39-amino acid peptides isolated from Heloderma Suspectum lizard venom that have different amino acids at positions 2 and 3, respectively (Eng J et al, 1992). Exendins are able to stimulate insulin secretion in response to rising blood glucose levels, and modulate gastric emptying to slow the entry of ingested sugars into the bloodstream. Exenatide exhibits 53% homology to native GLP-1. In comparison to Exenatide Liraglutide shows several key differences.

- **Liraglutide**
  - Human GLP-1 analogue
  - 97% homology to native GLP-1
  - Once daily
  - Can be taken without relation to meal timing
  - Safe in mild to moderate renal failure
  - Approved for use in combination with metformin, sulfonylureas & TZD's

In LEAD 6 study Buse JB et al evaluated once daily Liraglutide (1.8 mg) vs. Exenatide (10 mcg/day) in a head-to-head, 26-week open-label, parallel- group, multinational study. The primary outcome was change in HbA1c. Efficacy analyses were by intention to treat.

Liraglutide reduced mean HbA1c significantly more than did Exenatide (-1.12% vs -0.79% ; estimated treatment difference -0.33; p<0.0001) and more patients achieved a HbA1c value of less than 7% (54%vs 43%, respectively; odds ratio 2.02; p=0.0015). Liraglutide reduced mean fasting plasma glucose more than did Exenatide (-29 mg/dl vs -11 mg/dl; estimated treatment difference - 18.2 mg/dl; p<0.0001) but postprandial glucose control was less effective after breakfast and dinner. Both drugs promoted similar weight losses (Liraglutide -3.24 kg vs Exenatide -2.87 kg). Both drugs were well tolerated, but nausea was less persistent (estimated treatment rate ratio 0.448, p<0.0001) and minor hypoglycaemia less frequent with liraglutide than with exenatide (1.93 vs 2.60 events per patient per year; rate ratio 0.55; p=0.0131; 25.5%vs 33.6% had minor hypoglycaemia). Two patients in the exenatide group had a major hypoglycaemic episode. After 26 weeks patients on twice exenatide were shifted to once daily liraglutide in an open label extension for next 14 weeks (Buse JB et al, 2010). Switching from exenatide to liraglutide further and significantly reduced A1C (0.32%), FPG (16.2 mg/dl), bodyweight (0.9 kg), and SBP (3.8 mmHg) with minimal minor hypoglycemia (1.30 episodes/patient- year) or nausea (3.2%). Among patients continuing liraglutide, further significant decreases in bodyweight (0.4 kg) and SBP (2.2 mmHg) occurred with 0.74 episodes/patient-year of minor hypoglycemia and 1.5% experiencing nausea. In summary liraglutide once a day provides significantly greater improvements in glycaemic control than did exenatide twice a day, and is better tolerated.

- **Exenatide**
  - Exendin-4 analogue
  - 53% homology to native GLP-1
  - twice daily
  - To be taken before meals
  - Safety in renal failure not established
  - Approved for use in combination with metformin and sulfonylureas

Liraglutide (1.2 mg /day and 1.8 mg/day) has also been compared against DPP-4 inhibitor sitagliptin (100 mg/day) in a head-to-head parallel- group, open-label trial as adjunct treatments to metformin (Pratley RE et al, 2010). Greater lowering of mean HbA1c was achieved with 1.8 mg liraglutide (-1.50%) and 1.2 mg liraglutide (-1.24%) than with sitagliptin (-0.90%). Estimated mean treatment differences for liraglutide versus sitagliptin were -0.60% (p<0.0001) for 1.8 mg and -0.34% (p<0.0001) for 1.2 mg liraglutide. Nausea was more common with liraglutide (59 [27%] patients on 1.8 mg; 46 [21%] on 1.2 mg) than with sitagliptin (10 [5%]). Minor hypoglycaemia was recorded in about5% of participants in each treatment group. In conclusion Liraglutide was superior to sitagliptin for reduction of HbA1c, and was well tolerated with minimum risk of hypoglycaemia.

CONCLUSIONS

Currently, the need for antidiabetic therapies with fewer adverse effects (eg, weight gain, reduced rates of hypoglycemia) is unmet. In comparison to traditional options newer incretin-directed therapies treat the key metabolic abnormalities associated with T2DM but do so with reduced rates of hypoglycemia and do not promote weight gain as compared with conventional therapies. Once daily Liraglutide, the first human GLP-1 analogue, has shown excellent efficacy and safety profile throughout clinical development program. Liraglutide is also superior to other incretin based therapies like twice daily Exenatide and DPP-4 inhibitor sitagliptin. Liraglutide is a promising addition to physician's armamentarium against type2 diabetes.

END NOTE

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