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INCRETIN ANALOGUE, LIRAGLUTIDE A NEWER TREATMENT APPROACH FOR TYPE-2 DIABETES MELLITUS.

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ABSTRACT

Glucagon-like peptide 1 (GLP-1) receptor agonists, are one among the latest addition of medication included for the management of type 2 diabetes. Liraglutide, a novel long acting glucagon-like peptide analogue, is effective at improving indices of glycemic control. It has good tolerability and safety profile. It acts in a glucose-dependent manner. In controlled trials, it was observed that it produce short –term glucose lowering effects, with the reduction of HbA1C of up to 1.3 % which is comparable with oral agents. The beneficial effects observed for liraglutide was on reduction of weight (1-3.4 kg) and blood pressure (2.1-6.7mmHg). The formation of antibodies against Liraglutide was comparatively less than that of exenatide. The effects of liraglutide on beta-cell function, cardiovascular risk and disease progression are anticipated from long-term clinical trials results. There are on-going or in development trials exploring the effects of liraglutide in prediabetes, obesity and type 1 diabetes.

KEY WORDS: Incretin, GLP-1 analogue, Liraglutide.

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INTRODUCTION

One of the major public health problem, worldwide today is Type 2 Diabetes Mellitus (T2DM). It is associated with substantial morbidity and mortality. It has been reported as the leading cause of blindness, end-stage renal disease, lower extremity amputations and cardiovascular diseases. Day by day the disease rate is progressing. There is an increase in number of DM cases in young age also. It affects the quality of life of patients. Life style modification alone become unsuccessful in long run to control even type II diabetes mellitus and demands pharmacotherapy. Earlier the only therapeutic intervention available was the insulin secretagogues like sulfonylureas, glinides and insulin. After the introduction of metformin (biguanides) and other insulin sensitizers proved that they have an effect not only on glycemic control, but also on lipid metabolism . Metformin is the sole agent in the biguanide class of medication and it was found to cause weight loss and also decrease fasting glucose levels, thereby reducing HbAlc levels. A rare but potentially fatal complication of metformin therapy is lactic acidosis.

The other group, thiazolidinedione (TZD), pioglitazone, reduce the HbAlc in the order of 1 to 2 percentage. Fluid retention and weight gain have been the main adverse effect. Acarbose and miglitol are alfa-glucosidase inhibitors which acts in the intestinal lumen. The overall glycemic reduction is moderate and major adverse effects are abdominal floating and cramping frequently leading to cessation of drug use. Insulin replacement and supplementation strategies aim to replicate endogenous stimulated and basal insulin release by the healthy pancreas. The adverse effects of insulin therapy are weight gain, hypoglycemia and lipoatrophy. The current strategy is of using combination therapy with oral antidiabetic agents with different mechanism of action to achieve the target blood glucose level. The Optimal control of glucose is not achieved in most of the cases even with the advanced options for the treatment of diabetes The recent, investigational once daily oral medication for the treatment of type 2 diabetes in adults is Canagliflozin.It is a selective sodium glucose co-transporter 2 (SGLT2)inhibitor and acts by blocking the reabsorption of glucose by the kidney. This increases glucose excretion and lowers blood glucose levels in people with diabetes. Weight gain and hypoglycaemia interferes with many antidiabetic medications even with the longterm application of intensive therapies. Amongst newer drugs, one that has attracted more attention is Incretin based therapy.

INCRETIN BASED THERAPY

The oral administration of glucose in healthy non diabetic subject was found to produce a substantially enhanced insulin response compared with intravenous administration of glucose. This discrepancy is often called the incretin effect. There are two primary gut derived hormones that are responsible for most of the incretin effect. Incretins, Glucose Dependent insulinotropic polypeptide (GIP) and glucagon like peplide-1 (GLP) stimulate pancreatic cells to increase insulin secretion in response to oral carbohydrates. The secretion of GIP remains normal but the insulin response to it is impaired in T2DM. In T2DM, GLP-1 concentrations are reduced but the pancreatic response is relatively preserved. GLP-1 suppresses glucagon secretion. The two fundamental components of the regulatory mechanism that control glucose homeostasis are pancreatic α cells and glucagon secretion [1,30]. The regulation of glycemia is achieved by the secretion of glucagon by pancreatic α cells. The main action of this hormone is to counteract hypoglycaemia and insulin actions by stimulating hepatic glucose synthesis and mobilization; thereby concentration of blood glucose is increased. It inhibits gastric emptying, reduces appetite and intake of food [2,31]. It suppresses food intake through a pathway involving vagal different fibres signalling to regions of the brainstem of hypothalamus [3]. The principal problem with GLP-1 as a diabetic agent is that the N-terminal is rapidly cleaved by the enzyme, deptidyl peptidase - 4 (DPP-4) and this result in the generation of inactive amide. As a result GLP-1 has an in vivo half- life of less

than 2 minutes. Two approaches have made changes to allow therapeutic agents to prevent rapid degradation : Incretin mimetics and DPP-4 inhibitors. In both cases the half-life of GLP-1 to be prolonged. This can be achieved either by mobifying the molecule or by inhibiting DPP-4.[4,5,32] .

The DPP-4 inhibitors saxagliptin, linagliptin, sitaglipltin and vildagliptin reduce glycated hemoglobin by 0.5 to 1%. They have infrequent side effects but no effect on weight [6,7]. The available GLP-1 analogs are exenatide and liraglutide. The recently developed, GLP-1 agonist, Lixisenatide was on clinical trials as of September 2010. It has granted marketing authorization in Europe on February 2013. Exenatide is used as an adjunctive therapy for patients with type II diabetes who are taking metformin and /or a sulfonyl urea or a TZD or without metformin. Exenatide is a synthetic version of exendin - 4, 9 molecule that is found in the saliva of the Gila monster. It is detectable with in the plasma 15 minutes after subcutaneous injection. It remains detectable for up to 15 hours. It is administered subcutaneously since it is a peptide and degrades rapidly in the stomach. Exenatide is not recommended for use in patients with severe renal impairment (creatinine clearance ≤ 30 ml/minute) or end stage renal disease. Previous data showed some cases of hemorrhagic or necrotizing pancreatitis associated with exenatide therapy. Information regarding acute pancreatitis risk was added to the exenatide product label in the united states in 2007. In 27 % to 47 % patients treated with exenatide, antiexenatide antibodies was found [8,9].

LIRAGLUTIDE

Liraglutide is produced by DNA recombinant technology and it is a long acting GLP-1 mimetic agent similar to exenatide.It has 24 hr duration of action. It lowers fasting and postprandial blood sugar level and hence glycaemic control is improved. It is available in prefilled pens. The initial dose is 0.6mg once daily. It is administered for one week. The dose is increased after one week to 1.2 mg once daily for one week. The dose can be increased to 1.8 mg daily, if the blood glucose remains above the goal range. It can be added to existing metformin or to a combination of metformin and thiazolidinedione therapy. The dose of metformin and TZD remain unchanged. It can be added to sulfonyl urea therapy or to a combination of sulfonyl urea and metformin. When added to sulfonyl urea therapy, the dose of sulfonyl urea to be reduced inorder to prevent the risk of hypoglycaemia. When combined with the sulfonyl urea therapy, blood glucose self – monitoring is recommended to adjust the dose of sulfonyl urea therapy.

EFFECT ON GLYCEMIC CONTROL.

After 12 weeks of treatment , the effect was increased with liraglutide . At the end of 12-weeks treatment period, there was a largest decrease in HbA1C level. It was found that the HbA1C levels were still decreasing at the treatment period at these dosages. By observing HbA1C, the effect of the highest dosages of liraglutide was comparable with that of glimepiride with respect of fasting serum glucose.

LEAD TRIALS (LIRAGLUTIDE EFFECT AND ACTION IN DIABETES)

The longer duration clinical studies was initiated by the manufacturers to define the role of liraglutide in the treatment of diabetes by a programme known as LEAD. [9]. In all the six trials, the immunogenicity to liraglutide was assessed. The antibody assays was used to measure and characterise anti-liraglutide antibodies.[10,11]. The main objective of these analyses were to

1) Measure and characterise antibody formation to liraglutide
2) Investigate the impact on glycemic control and safety.
3) Compare the frequency of antibody formation to liraglutide and exenatide.
4) Assess the impact of antibody formation on clinical efficacy of each of the peptides.
5) To find out the glycemic response to liraglutide due to the effect of continual anti-exenatide antibodies mainly in patients those who are shifting from exenatide to liraglutide therapy.

The existing oral hypoglycaemic therapies was compared with liraglutide in the LEAD

programme. It was done either using a single agent or as combination..In LEAD 3 trial ,the comparison of Liraglutide was with sulfonylurea, glimepride[12,13.] Liraglutide was added to other oral hypoglycaemic agents in LEAD 1,2,& 4 studies. Liraglutide and Insulin glargine were compared as add on therapy with glimepride & metformin in LEAD - 5 [14]. The Lead 6, was an open –label head-to-head trial comprising of 26 week and compared liraglutide with exenatide on addition with metformin and/or glimepride[15,16]. The proportions of patients between 35 & 58% for liraglutide 1.2 mg achieved American Diabetes Association (ADA) HbA1C target <7%. For liraglutide 1.8 mg, it was found between 42 & 54 %. There was also considerable reduction in Fasting plasma glucose (FPG) levels across all the studies.The mean postprandial plasma glucose (PPG) was also reduced in all LEAD studies[17.]The greatest reduction of PPG was observed in LEAD - 4 , liraglutide plus rosiglitazone and metformin.

EFFECT ON BODY WEIGHT

It was found that there was no increase in body weight with Liraglutide treatment. There were related study which experienced significant weight loss on the majority of liraglutide treated T2DM subjects. The trial and treatment group were analysed with 26 week data from 7 phase 3, randomized trials in the liraglutide T2DM development programme. Liraglutide (1.2 & 1.8mg) active comparator & placebo outcome measures included proportion of subjects in various weight change categories and their % weight change from baseline; impact of body mass inde (BMI) & gastro intestinal adverse events on weight change and correlation of weight change with change in HbA1c.(6) It was more in GLP-1 agonist –treated subjects, taking Liraglutide versus active comparator [18, 19]. In Astrup and colleagues trial, obese people were randomly assigned to receive liraglutide (1.2mg, 1.8 mg, 2.4 mg or 3.0 mg once a day by subcutaneous injection, n=90-95), placebo (once a day by subcutaneous injection, n=98) or orlistat (120mg three times a day orally,n=95) .There was a constant, clinically relevant weight loss (dose dependent) by treating people with liraglutide. It was significantly greater than that with placebo and orlistat (vs liraglutide 2.4mg and 3.4 mg). There was mean weight loss with liraglutide 3.0 mg was 7.2 kg. Nausea and vomiting were more frequent with liraglutide but the events were mostly transient and of mild or moderate intensity [20, 21].

EFFECT ON BLOOD PRESSURE

An unexpected but consistent effect of liraglutide in the liraglutide effect and action in Diabetes (LEAD) programme was the reduction of blood pressure .The reduction was modest and ranging from 2.1 to 6.7 mm Hg. From this observance, the reduced GLP-I secretion may be contributing factor to the increased prevalence of hypertension among patients with T2DM [22].

EFFECT ON ISLET CELL FUNCTION

After 12 weeks of Liraglutide treatment, HOMA (Homeostasis model assessment) was used to assess β-cell function and insulin resistance. After 12 weeks, Mean β cell function was significantly higher in the highest dosage group than in the placebo group [23]. Liraglutide preserves pancreatic beta cells in diabetic mice. To investigate the molecular mechanism by which liraglutide preserves pancreatic beta cell mass, they treated obese diabetic db/ db mice with liraglutide for 2 days or 2 weeks. They also treated normoglycaemic m/m mice with liraglutide for 2 weeks. There was improved metabolic variables and insulin sensitivity in diabetic in db/dbmice after 2 weeks of Liraglutide treatment. It also increase glucose-stimulated insulin secretion and islet insulin content in both mouse strains and reduced triacyl glycerol content in db/db mice.The beta cell mass is increased with liraglutide.It is by directly regulating cell kinetics and by suppressing oxidative stress. However further studies are needed to fully understand the effect of liraglutide on peptide expression and function ,as well as its role in neogenesis from the ducts .The beneficial effects of Liraglutide in preserving β cell function should be assessed further in humans[24].

SAFETY EVALUATION.

It shows considerable promise as a once daily

long acting GLP-1 liraglutide therapy for lowering blood glucose without weight gain and substantial risk of hypoglycaemia. Adverse events were isolated. The most frequent adverse effect reported was headache and nausea. The events were transient and of mild or moderate severity and resolved without intervention. None of the patients withdraw due to nausea and vomiting. Most of the gastrointestinal events were transient. Since there is a risk of Pancreatitis with liraglutide , it should be used cautiously in patients. [25].

EXENATIDE VS LIRAGLUTIDE

Pharmcokinetic considerations suggest that the drug accumulation risk is less with liraglutide compared with exenatide [26, 27]. Exenatide treated patients was found to be at more risk of Pancreatitis. Hence, Liraglutide might be tolerated better by patients with diabetic nephropathy [28, 29].

CONCLUSION

Newer drugs Liraglutide and exenatide are longer acting GLP-1 receptor agonists associated with greater HbA1c lowering efficacy due to more predominant effects on fasting glucose level.. Liraglutide is administered once daily. It can administered without any restriction on timing or relation to meals. Liraglutide also causes dose dependent weight loss even in non-diabetic obese patients. Liraglutide appears to be slightly more effective in controlling blood glucose while comparing with exenatide. Liraglutide, shows improvements in blood pressure, diabetic dyslipidemia, hepatic steatosis markers and myocardial function. All these effects have the potential to reduce the burden of cardiovascular disease being the major cause of mortality in patients with T2DM

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