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GLUCAGON-LIKE PEPTIDE 1 RECEPTOR AGONISTS FOR TYPE 2 DIABETES-A REVIEW

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ABSTRACT

Targeting the incretin system has become an important therapeutic approach for treating type 2 diabetes. In people with type 2 diabetes mellitus (T2DM), the incretin effect is reduced, but the recent advent of dipeptidyl peptidase-4 inhibitors and glucagon-like peptide (GLP)-1 agonists/analogues has enabled restoration of at least some of the function of the incretin system, with accompanying improvements in glycaemic control.[1] The physiological response to oral ingestion of nutrients, involving the incretin system, is reduced in some patients with type 2 diabetes but may be augmented by administration of GLP-1 receptor agonists. Two GLP-1 receptor agonists/analogues are currently approved for the treatment of T2DM— exenatide (Byetta®, Eli Lilly & Co., Indianapolis, IN, US) and liraglutide (Victoza®, Novo Nordisk, Bagsvaerd, Denmark); a once-weekly formulation of exenatide (Bydureon®, Eli Lilly & Co.) has also been approved by the European Medicines Agency. This review aims to investigate the effectiveness of GLP-1 analogues in patients with type 2 diabetes mellitus who are not achieving satisfactory glycaemic control with one or more oral glucose lowering drugs.[1,2]

KEYWORDS: Targeting the incretin system has become an important therapeutic approach for treating type 2 diabetes.

INTRODUCTION

The primary aim of treatment for type 2 diabetes is to control blood glucose and reduce the development of diabetes-associated secondary complications.[1] Over time, persistently elevated levels of plasma glucose (hyperglycaemia) lead to various microvascular (retinopathy, nephropathy and neuropathy) and macrovascular (cardiovascular diseases) complications. The risk of developing such complications is strongly associated with the period of exposure to hyperglycaemia.[2] Therefore, people with type 2 diabetes should be initially advised lifestyle modifications like weight loss, increasing physical activity, diet and offered ongoing patient education. If it fails, they should be switched to oral hypoglycaemic agents. In some cases, Metformin is mostly preferred over other drugs for uncontrolled hyperglycaemia. But there are certain side effects for the same which affects the patients' quality of life.[2]

GLP-1 analogues are a new class of glucose lowering drugs, given by injection, that mimic the action of an endogenous gastrointestinal hormone GLP-1, an incretin hormone that is released into the circulation in response to food. It regulates glucose levels by stimulating glucose dependent insulin secretion and biosynthesis, and by suppressing glucagon secretion, delaying gastric emptying and promoting satiety.[3] Intravenous administration of exogenous GLP1 to patients with type 2 diabetes was shown to reduce plasma glucose concentrations to the normal fasting range, even in patients who had an inadequate response to oral antihyperglycemic drugs. GLP-1 is an incretin hormone that helps maintain plasma glucose levels through regulation of insulin and glucagon. GLP-1 is also secreted by pancreatic islet cells and neurones in the brainstem. Incretin hormones potentiate glucose-induced insulin secretion and are responsible for around 70% of postprandial insulin secretion in healthy individuals, as well as inhibiting glucagon secretion from the pancreatic alpha-cells in the presence of hyperglycaemia, thereby reducing hepatic glucose output.[2,3] GLP-1 may also promote proliferation/neogenesis of pancreatic beta cells (animal data only).

GLP-1 has multiple physiological effects that make it a more attractive candidate for treatment of T2DM. Administration of pharmacological levels of GLP-1 analogues resistant to DPP-4, not only increases insulin secretion while inhibiting glucagon release in a glucose-dependent fashion, but also delays gastric emptying and suppresses food intake.[1,3] Exogenous administration of

GLP-1 to regulate blood glucose is a possible therapeutic solution for T2DM; however, once subcutaneously injected, the N-terminal of the naturally occurring GLP-1 molecule is rapidly cleaved by the DPP-4 enzyme, thus generating an inactive GLP-1-(9-36) amide, resulting in a very short half-life of approximately 1.5 min.[4] As such, the frequency of exogenous GLP-1 administration required to achieve therapeutic blood-glucose regulating effects is impractical. Current GLP-1 analogues approved for use in the United States and the European Union include: exenatide twice daily, exenatide once weekly, liraglutide once daily, lixisenatide once daily (not approved in the U.S.) and albiglutide once weekly, which are all delivered through subcutaneous injection and initial dose titration is required to improve gastrointestinal tolerance.[3,4]

For this review, we refer to "short-acting" GLP-1 receptor agonists as those agents having duration of action of, 24 h and "long acting" as those agents with duration of action 24 h (Table 1).

Short-acting <24 h	**Long acting ≥24h**	
Twice daily	Once daily	Once weekly
Exetanide (launched)	Liraglutide (launched)	Exenatide LAR (phase 3) Taspoglutide (phase 3) Albiglutide (phase 3) LY2189265 (phase 2)

[5]

GLP1 Receptor Analogues

Exenatide was the firstly introduced GLP1 analogue which is a polypeptide initially extracted from salivary glands of the Gila monster and has close homology (53%) to human GLP-1, but is resistant to DPP-4 degradation and thus has a prolonged duration of activity. Exenatide (also known as exendin-4) must be given parenterally. It is released from the gut and acts to increase glucose-dependent insulin secretion from pancreatic beta cells, suppress glucagon secretion, delay gastric emptying, and reduce food intake. The binding of the drug to pancreatic GLP-1 receptors mediates these actions.[5] Clinical trial results have demonstrated that exenatide, when used in combination with selected oral antidiabetic drugs, effectively reduces A1C by 20.4 to 21.5% in patients with type 2 diabetes inadequately controlled on metformin with or without a sulfonylurea. Across these studies, body weight was seen to decrease in a dose- dependent manner; treatment with 10 mg exenatide, as an add-on to metformin, resulted in the greatest weight loss (22.8 kg) in patients previously treated with metformin alone. Exenatide was generally well tolerated, with mild-to-moderate gastrointestinal effects being the most common adverse effect.[6]

Later on Liraglutide a once-daily human GLP-1 analogue was introduced with 97% homology with human GLP. Modifications to the liraglutide, such as attachment of a fatty acid chain with a glutamoyl spacer to a lysine residue and amino acid substitution, slow the absorption and delay the degradation of liraglutide by DPP-4, prolonging the half-life to 13 h. In addition to its glucose-lowering effects, data from clinical studies have now established that treatment with liraglutide leads to improvement of various risk factors, such as body weight, blood pressure and lipid panels.[6]

Recently, oral Semaglutide (Rybelsus) is the first oral glucagon-like peptide 1 (GLP-1) receptor agonist product approved by the U.S. Food and Drug Administration (FDA) for the treatment of type 2 diabetes. The primary advantage of this semaglutide formulation is its oral administration route, which makes it an option for patients who are unwilling or unable to self- inject glucose-lowering medications. Studies compared the addition of oral semaglutide or subcutaneous liraglutide to background metformin with or without a sodium–glucose cotransporter 2 (SGLT2) inhibitor in patients with type 2 diabetes and a baseline A1C of 7.0– 9.5%. After 26 weeks of treatment, oral semaglutide (target dose of 14 mg once daily) resulted in a mean A1C reduction from baseline of 1.2% compared with a reduction of 1.1% observed with liraglutide (target dose of 1.8 mg once daily), thus demonstrating noninferiority.[7]

Exenatide v/s other GLP1 Analogues

The GLP-1 analogues exenatide and liraglutide stimulate insulin secretion and inhibit glucagon output in a glucose-dependent manner, slow gastric emptying and decrease appetite. The injectable glucagon-like peptide-1 (GLP-1) receptor agonist exenatide significantly improves glycaemic control, with average reductions in HbA1c of about 1.0% point, fasting plasma glucose of about 1.4 mmol l, and causes a weight loss of approximately 2-3 kg after 30 weeks of treatment. The adverse effects are transient nausea and vomiting.[7] The long-acting once-daily human GLP-1 receptor agonist liraglutide reduces HbA1c by about 1.0-2.0% point, weight by 1-3 kg and seems to have fewer gastrointestinal side effects than exenatide. Also results of certain trials showed that efficacy of semaglutide was superior to exenatide for the improvement of glycemic control and reducing body weight. Semaglutide showed a decrease in HbA1c by 1.5% vs. 0.9% decrease with exenatide ER.[8]

GLP1 Analogues v/s DPP-4 inhibitors

Dipeptidyl peptidase-4 (DPP-4) inhibitors block the breakdown of GLP-1 and GIP to increase levels of the active hormones. In clinical trials, DPP-4 inhibitors have a modest impact on glycemic control. They are generally

well-tolerated, weight neutral and do not increase the risk of hypoglycemia. GLP-1 receptor agonists (GLP-1 RA) are peptide derivatives of either exendin-4 or human GLP-1 designed to resist the activity of DPP-4 and therefore, have a prolonged half-life. In clinical trials, they have demonstrated superior efficacy to many oral antihyperglycemic drugs, improved weight loss and a low risk of hypoglycemia. However, GI adverse events, particularly nausea, vomiting, and diarrhea are seen. Both DPP-4 inhibitors and GLP-1 RAs have demonstrated safety in robust cardiovascular outcome trials, while several GLP-1 RAs have been shown to significantly reduce the risk of major adverse cardiovascular events in persons with T2DM with pre-existing cardiovascular disease (CVD). Several clinical trials have directly compared the efficacy and safety of DPP-4 inhibitors and GLP-1 RAs. These studies have generally demonstrated that the GLP-1 RA provided superior glycemic control and weight loss relative to the DPP-4 inhibitor. Both treatments were associated with a low and comparable incidence of hypoglycemia, but treatment with GLP-1 RAs were invariably associated with a higher incidence of GI adverse events.[7,8,9]

Combining Basal Insulin Analogues with GLP-1 Mimetics

Basal insulin is a highly effective treatment in reducing fasting blood glucose. However, it is associated with considerable risk of hypoglycemia and weight gain. Because of these clinical concerns, basal insulin initiation and intensification is often delayed by prescribers. On the other hand, glucagon like peptide 1 receptor agonists (GLP-1 RAs) are also effective in terms of glycemic control (both fasting and postprandial) and associated with weight loss and low risk of hypoglycemia.[10] Traditionally, glycaemic control using insulin regimens has been achieved with basal insulin to target FPG, followed by the addition of bolus insulin to cover PPG excursions, if required. However, very intensive insulin regimens are associated with a higher risk of hypoglycaemia and weight gain, which can be a burden on patients.[11]

Adverse Events Associated with GLP-1 Receptor Analogues

The most common adverse events noted with clinical use of GLP-1R agonists include nausea, vomiting, and diarrhea, likely reflecting central aversive actions of GLP-1 control of gut motility. Regulatory concerns surrounding the risk of thyroid C-cell hyperplasia and medullary thyroid carcinoma (MTC) were based entirely on data from mice and rats, which express the canonical GLP-1R on thyroid C cells, linked to stimulation of calcitonin secretion and C-cell proliferation. In contrast, it is difficult to detect GLP-1R expression within primate thyroid C cells, and sustained GLP-1R agonism does not induce C-cell hyperplasia in monkeys. Indeed, associated reports of GLP-1R expression within the normal and neoplastic human thyroid reflected the use of nonspecific, incompletely validated GLP-1R antisera not suitable for detection of the GLP-1R.[12] Subsequent assessment using a validated GLP-1R antibody to analyze 44 different normal and tumorous human thyroid glands did not detect GLP-1R expression by immunocytochemistry in normal thyroid C cells nor in the majority of MTC cases examined . Moreover, extensive clinical follow-up coupled with thousands of calcitonin measurements have failed to reveal evidence for a functional GLP-1R C-cell axis or MTC in human subjects with diabetes or obesity treated for several years with long-acting GLP-1R agonists.

The possibility that therapy with GLP-1R agonists might predispose susceptible individuals to the development of acute or chronic pancreatitis or pancreatic cancer has received considerable scrutiny. These concerns initially arose following clinical reports of acute pancreatitis in human subjects treated with exenatide. Simultaneously, histological studies reported GLP-1R expression within pancreatic ducts and preneoplastic lesions in animals and humans, and preclinical experiments linked incretin signaling to pancreatic inflammation and cell proliferation in rodents. Notably, efforts to reproduce many of these preclinical findings were unsuccessful, reflecting limitations of many of the reagents and experimental designs used in these studies.[13] Subsequent examination of a large number of pancreata from different strains of rats revealed spontaneous rates of histological abnormalities, including pancreatitis, in up to 72% of animals never exposed to incretin therapy. Although small rises in plasma lipase and, to a lesser extent, amylase have been reported in some human subjects with diabetes treated with GLP-1R agonists, these observations reflect direct activation of the canonical pancreatic acinar cell GLP-1R coupled to enzyme secretion, and not subclinical pancreatitis.

The safety of GLP-1R agonists has also been scrutinized in multiple CVOTs, which failed to generate a signal linking sustained therapy with GLP-1R agonists to pancreatitis or thyroid or pancreatic cancer. Similarly, in 2,024,441 person-years of follow-up, examination of health records failed to reveal increased reports of pancreatic cancer in individuals treated with incretin-based therapies. Given the long latency required for cancer signals to emerge, coupled with the low incidence rates for malignancies such as MTC, it is not yet possible to completely exclude the possibility that a cancer signal might yet emerge in longer, larger studies or following scrutiny of more extensive drug exposure using electronic health databases.[14,15]

CONCLUSION

Agents in the GLP-1 receptor agonist class are effective treatment options for patients with type 2 diabetes, achieving reductions in A1C and body weight as monotherapy or as an add-on to other antihyperglycemic therapies, including insulin. Short-acting analogs Exenatide and lixisenatide have a predominant effect on postprandial glucose while long-acting analogs like

Liraglutide, Exenatide ER, albiglutide and Dulaglutide have a predominant effect upon fasting blood glucose. GLPs induction of weight loss is an additional plus point as obesity is very common sign in T2DM, semaglutide and Itca-650 (sustain release.) GLP-1 agonists significantly reduce body weight and HbA1c while other categories of drugs of DPP-4 inhibitors are weight neutral. Although, there are concerns regarding the use of GLP- 1 agonists and acute pancreatitis, preclinical and clinical studies have demonstrated no clear- cut link between the use of GLP-1agonists and risk of pancreatitis in type 2 diabetic patients. In the future GLP-1 agonists may become the most preferred drugs for the treatment of diabetes and surpass currently available drugs for diabetes.

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