A brief review on newer Glucagon like Peptide-1 analogues

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Abstract

GLP-1 (Glucagon like Peptide-1) receptor agonists have been shown to be effective in the treatment of type 2 diabetes mellitus (T2DM). Although the first GLP-1 receptor agonist, Exenatide, was approved in the year 2000, other agents with a longer duration of action that do not require twice-daily dosing are now being developed. Indeed, Liraglutide, a once-daily GLP-1 receptor agonist, was approved in 2010, a once-weekly extended-release formulation of Exenatide (Exenatide ER) was approved in 2011 and now more recently Semaglutide, an oral GLP 1 receptor agonist was approved for medical use in the United States in September 2019 and in the European Union in April 2020. The importance of GLP-1 itself and the use of GLP-1 receptor agonists in T2DM are discussed. An overview of the clinical development of the GLP-1 receptor agonists (Exenatide ER, Liraglutide, Lixisenatide, Albiglutide, Taspoglutide and Semaglutide) is provided and their mechanism of action, efficacy in terms of glycaemic control, weight loss and tolerability are reviewed.

Keywords: GLP1 receptor agonist; Liraglutide; Exenatide ER; Lixisenatide; Semaglutide

Introduction

Diabetes Mellitus

Diabetes mellitus is one of the most challenging health problems worldwide with an alarming increase in its prevalence and associated conditions such as hypertension, dyslipidaemia and cardiovascular disease. It is one of the main threats to human health and a chronic metabolic disorder that results from defects in either insulin secretion and/or insulin action or both. An elevated rate of basal hepatic glucose production in the presence of hyperinsulinemia is the primary cause of fasting hyperglycaemia after a meal. Impaired suppression of hepatic glucose production by insulin and decreased insulin-mediated glucose uptake by muscle contribute almost equally to postprandial hyperglycaemia. (1)

Epidemiology

The total number of people with diabetes worldwide was estimated between 151 million and 171 million in 2000 and is projected to increase to 221 million in 2010 and to 366 million in 2030 (2). Needless to say, the increase in the number of people with diabetes will be accompanied by an increase in the
number of those with diabetic complications such as nephropathy, retinopathy, neuropathy and atherosclerosis. Hence, throughout the world, the prevalence of type 2 diabetes mellitus has increased dramatically in the past two decades.

Pathophysiology

The biochemical and physiological processes that underlie T2DM are still unclear, although most certainly involve impairment in insulin secretion and insulin action at the periphery. Chronic hyperglycaemia results from these defects due to which the patients with diabetes experience significant morbidity and mortality from microvascular (retinopathy, nephropathy and neuropathy) and macrovascular (heart attacks, stroke and peripheral vascular disease) complications. The core pathophysiology of T2DM has been attributed to the classic triad of decreased insulin secretion, increased insulin resistance and elevated hepatic glucose production. Research has shown that additional mechanism with type 2 diabetes include those related to fat cells (accelerated lipolysis), GIT (Incretin deficiency / resistance), α-cell (hyperglucagonemia), kidney (increased glucose reabsorption) and brain (insulin resistance) referred to as the "ominous octet". Given that type 2 diabetes accounts for more than 90% of cases of diabetes worldwide, it is important that we understand the pathogenesis of this condition and develop new approaches to its prevention and treatment. Despite a broad range of effective blood glucose-lowering therapies, almost half of T2DM patients are not reaching recommended glycaemic targets. Conventional T2DM therapies are effective at lowering blood glucose but they do not impact upon the progressive decline of β-cell function, so glycaemic control continues to deteriorate unless treatment is intensified. In addition, most conventional T2DM therapies are associated with weight gain and/or hypoglycaemia, which pose significant barriers to treatment intensification.

GLP-1 Analogues- Novel Therapeutic Option: Background

There is evidence that nutrient-induced secretion of the glucose regulating incretin hormone i.e. glucagon-like peptide-1 (GLP-1) is impaired in diabetes mellitus. The potential of GLP-1 as a therapy target for type 2 diabetes has gained increasing attention in recent years. This insulinotropic hormone is released from the L cells in the intestine in response to meals to stimulate insulin secretion and decrease glucagon secretion. Hence, GLP-1 has the potential to be harnessed as a type 2 diabetes treatment that lowers blood glucose with a low risk of hypoglycaemia. GLP-1 also decreases gastric emptying rate and appetite that are therapeutically desirable to be given in patients of diabetes mellitus and obesity in association with insulin resistance. Native GLP-1 is however rapidly metabolized by enzymes such as dipeptidyl peptidase-IV (DPP-IV), giving it a very short half-life of less than 2 min and limiting its potential to be developed as a therapeutic agent. Hence, analogues or mimetic of GLP-1 with a prolonged activity are therefore required in order to exploit successfully the actions of GLP-1 in the treatment of diabetes.

Incretins

Incretins are a group of hormones that includes Glucagon like peptide-1 (GLP-1) and Glucose dependent insulinotropic polypeptide (GIP) that are released after meals from the upper and lower bowel. These incretins augment glucose dependent insulin secretion, during the phase of nutrient absorption from the GIT. Among them, GLP-1 is the prominent insulinotropic incretin, which has a very short half-life (1-2 min) due to its quick metabolism by DPP-IV enzyme.

Glucagon Like Peptide-1 (GLP-1)

Glucagon like peptide-1 (GLP-1) is an incretin hormone released from intestinal L-cells into the circulation in response to dietary nutrient intake. It increases β-cell insulin secretion and reduces alpha cell glucagon secretion in a glucose dependent manner. In recent years, considerable interest has focused on the potential of GLP-1 as a novel treatment strategy for type 2 diabetes. Patients with long-standing T2DM seem to have reduced levels of GLP-1. In such patients glucagon like peptide-1 (GLP-1) concentrations are reduced in response to a meal, whereas glucose dependent insulinotropic polypeptide concentrations are normal or increased. This observation suggests resistance to the actions of glucose dependent insulinotropic polypeptide making GLP-1 the favoured potential therapeutic target. The most important action of GLP-1 occurs in the pancreas. Its receptors have been located in β, α and δ-cells. Exogenous administration of GLP-1 at pharmacological doses has been shown to increase insulin secretion, reduce glucagon secretion and blood glucose in T2DM patients as well as decreased gastric emptying and reduced food intake leading to weight loss.

Many of the pathophysiologic disturbances that are present in T2DM can be corrected by incretin replacement with GLP-1. In response to the physiologic loss of incretin activity associated with T2DM, administration of exogenous GLP-1 has been shown to lower both fasting and postprandial plasma glucose significantly. The main limitation in developing GLP-1 for the treatment of T2DMis its short half-life of fewer than two minutes as dipeptidyl peptidase-4 (DPP-4) rapidly inactivates GLP-1 by removing two N-terminal amino acids. The development of the GLP-1receptor agonists offers incretin-based therapies with built-in modifications to
provide resistance to DPP-4 degradation.\(^{(16)}\)

It had been demonstrated that glucagon secretion in T2DM is not suppressed after a carbohydrate-rich meal\(^{(18)}\). This results in an inability to suppress postprandial hepatic glucose production and excessive plasma glucose excursions. The rate of gastric emptying is a key determinant of postprandial glucose excursions and is often accelerated in people with diabetes.\(^{(19)}\) GLP-1 signalling increases satiety and slows gastric motility and secretion further contributing to a reduction in food intake. Furthermore, GLP-1 has been shown to increase cell differentiation, proliferation and insulin synthesis and lowers triglycerides in T2DM rats.\(^{(20)}\)

This considerable clinical interest derived from GLP-1 having a rather large spectrum of effects, all working in favour of efficacious lowering of blood glucose and simultaneous lowering of body weight with a low risk of hypoglycaemia.\(^{(21)}\) The two drugs most advanced in this regards are exenatide and liraglutide, both of which must be administered by subcutaneous injection.\(^{(22)}\) As GLP-1 mimetics must be administered by injection, their place in antihyperglycaemic therapy is probably as add-on treatment for patients who can no longer achieve blood glucose control with combinations of oral agents.

**Newer Glucagon Like Peptide-1 Analogues:**

Liraglutide, Exenatide ER, Lixisenatide, Albiglutide, Taspoglutide, Semaglutide, Efpeglenatide, Dulaglutide.

**Liraglutide**

Liraglutide is a modified form of human glucagon like peptide 1 (GLP-1) analogue, was FDA approved and licensed for treating adults with type 2 diabetes mellitus.\(^{(23)}\) It has the potential to acquire an important role not only in the treatment of diabetes but also in the preservation of \(\beta\)-cell function, weight loss and prevention of chronic diabetic complications. The drug reduces plasma glucose levels in both fasting and postprandial state, thus achieving improvement in hemoglobinA1c (HbA1c). Liraglutide has been shown to increase cell differentiation, proliferation and insulin synthesis and lowers triglycerides in T2DM rats.\(^{(20)}\)

The drug increase insulin secretion from \(\beta\)-cells thereby decreasing the elevated blood glucose levels. Its effects on \(\beta\)-cells are mediated by a G-protein-linked receptor that involves cAMP formation and protein kinase A (PKA) activation to bring about the closure of ATP-sensitive \(K^+\) channels in a synergistic interaction with glucose, a phenomenon called glucose competence.\(^{(24)}\) This causes membrane depolarisation and the opening of \(Ca^{2+}\) channels, which triggers insulin exocytosis. The inhibition of gastric emptying decreases glucose excursion after meals by reducing incremental glucose and insulin response. Moreover physiologically, this mechanism outweighs pancreatic insulinotropic GLP-1 effects after intake of a meal. Delay in gastric emptying is probably mediated by vagal inhibition as shown by the loss of this effect in vagotomised humans. This action may occur via GLP-1 interaction with receptors in the CNS or to afferent neural pathways to the brain stem.\(^{(24)}\)

Pharmacokinetic studies show that liraglutide after a subcutaneous injection has a time to maximum plasma concentration (\(T_{\text{max}}\)) of 9–13 hours and a half-life of 13 hours.\(^{(25)}\) Following subcutaneous injection, the fatty acid chain allows liraglutide to self-associate and form heptamers at the injection site depot.\(^{(25)}\) It is thought that the size of the heptamer and strong self-association are the most likely mechanisms by which delayed absorption of liraglutide from the subcutaneous tissue is facilitated. Once in the bloodstream, the fatty acid chain allows reversible binding to serum albumin, providing partial stability and resistance to metabolism by DPP-4 and reduces renal clearance giving liraglutide a protracted mechanism of action.\(^{(25)}\)

Clearance of native GLP-1 and its metabolites is largely mediated via the kidneys.\(^{(25)}\) The renal filtration and clearance of liraglutide are largely prevented by high binding to albumin and metabolic stabilization. Thereby liraglutide is fully metabolized in the body by sequential cleavage of small peptide fragments and amino acids, which involves DPP-IV and neutral endopeptidase and clearance of liraglutide are suggested to take place by multiple organ or tissues.\(^{(25)}\) Liraglutide is thus comparable with a large peptide, with no single organ acting as the major route of elimination and hence hepatic impairment is not expected to lead to increased exposure.\(^{(26)}\)

In the liraglutide clinical trial program, there were seven cases of pancreatitis among liraglutide treated patients and one case among comparator treated patients (2.2 vs. 0.6 cases/1000 patient years).\(^{(27)}\) Five cases with liraglutide were reported as acute pancreatitis and two cases with liraglutide were reported as chronic pancreatitis. The FDA deemed there to be too few cases to determine whether liraglutide caused pancreatitis and a special warning was added to reflect a

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possible link with pancreatitis.\(^{28}\) It is recommended that all GLP-1 receptor agonist therapies are promptly discontinued if pancreatitis is suspected and not restarted if pancreatitis is confirmed and alternative glucose lowering therapies should be considered in patients with a history of pancreatitis.\(^{29}\)

In preclinical studies, C-cell carcinoma was observed in rats treated with Liraglutide and mice treated with very high doses of Liraglutide.\(^{30}\) Concentrations of calcitonin, a biomarker of C-cell activation was elevated in these animals. Calcitonin concentration was monitored in more than 5000 T2DM or obese non-diabetic patients from nine clinical trials of liraglutide and no significant differences were observed between liraglutide treated and comparator treated patients.\(^{31}\) The observations in rodents are thought to be a consequence of a 22 to 45 fold higher density of C-cells in rodent versus human thyroid glands and a 15 to 124fold greater density of GLP-1 receptors on rodent C-cells compared with human C-cells.\(^{32}\)

More data are required to provide reassurance about current safety concerns surrounding this class of therapies including the risk of pancreatitis, C-cell carcinoma and cardiovascular safety. Liraglutide and exenatide are now being investigated as potential weight loss therapies. While liraglutide is undergoing Phase III trials as a general obesity therapy, Exenatide is now being studied in a number of defined phenotypes of obesity such as Prader Willi syndrome, hypothalamic obesity, pediatric obesity, olanzapine induced obesity and polycystic ovary syndrome.\(^{33–35}\)

Liraglutide provided additional glycaemic control when added to intensive insulin therapy in T1DM patients.\(^{36}\) In a separate study, it allowed insulin doses to be reduced while maintaining or further improving glycaemic control.\(^{37}\) The long term effects of GLP-1 were observed in a 6-week pilot study comparing GLP-1 subcutaneous infusion with saline. In the GLP-1 group, fasting plasma glucose (FPG) dropped by 4.3 mmol/l and the 8 hr. mean plasma glucose by 5.5 mmol/l.\(^{38}\) Glycosylated haemoglobin (HbA1c) decreased by 1.3%. The fasting free fatty acid concentration decreased by 30% and the 8 hr. mean concentration by 23%. Bodyweight decreased by 1.9 kg, gastric emptying was inhibited and food intake was reduced, although no significant changes were observed in the saline group.\(^{38}\) Hence, GLP-1 has shown many predicted therapeutic properties, blood glucose is lowered with a low risk of hypoglycaemia and a concomitant decrease in body weight.\(^{39,40}\)

The effect of the injection site (abdomen, upper arm and thigh) on the pharmacokinetic profile of liraglutide was investigated.\(^{41}\) It was found that based on the area under the concentration-time curve (AUC), the abdomen and thigh were equivalent. However, lower bioavailability was observed in the thigh compared with the abdomen. Based on these results, the differences in bioavailability were not considered clinically relevant and the three injection sites can be used interchangeably. Age and gender pharmacokinetic equivalence of subcutaneous liraglutide 1mg/day demonstrated that when adjusted for body weight, the similarity was confirmed between young and elderly subjects and no significant effect on gender was observed.\(^{42}\) Furthermore, the reduction in HbA1C is associated with the beneficial effects of liraglutide in insulin resistance, systolic blood pressure and weight loss, as shown by the LEAD (Liraglutide effect and action in diabetes) studies could represent a significant probability of prevention of diabetic complications.\(^{23}\) Liraglutide may have the ability to change food preferences and thus reduce energy intake in human beings as well.\(^{39}\) When it was given as a 1.8 mg daily dose reduced hunger in two studies.\(^{43}\) A similar dose was noted to reduce food intake in one of these studies where Liraglutide 1.2 mg and 1.8 mg have been found to reduce body weight.\(^{43}\)

Available preclinical and clinical data clearly demonstrate the utility of liraglutide in reducing weight, thus making it a drug of choice for obese patients with diabetes.\(^{43}\) The correction of this important part of insulin resistance syndrome should lead to improved cardiovascular outcomes. Moreover, it was observed in a study that liraglutide 1.8 mg and 1.2 mg reduced Systolic blood pressure by 3.6 mmHg and 2.1 mmHg respectively.\(^{44}\) Non-significant decrease in diastolic blood pressure was reported in the same study. These results have led to the realization that liraglutide is effective not only in correcting hyperglycaemia but also has blood pressure lowering pleiotropic effect. Similar results have been reported from other LEAD trials, where liraglutide has been studied in combination with other drugs.\(^{23}\) Liraglutide 1.8 mg has demonstrated the lowering of systolic blood pressure by 1.4–4.5 mmHg in LEAD-1, 2 and 5, reaching statistical significance in the latter (P < 0.05).\(^{45}\) The reduction noted with liraglutide was significant when compared with the reduction of systolic blood pressure seen with placebo in LEAD-4. No significant change in diastolic B.P. has been noted.\(^{45}\)

Furthermore, Liraglutide has been shown to reduce triglyceride levels without affecting the concentration of other lipids. This makes it an attractive choice for patients with diabetic dyslipidaemia, which is characterized by high levels of triglycerides. While no long-term data of cardiovascular outcomes is available however other studies show a cardioprotective effect of liraglutide.\(^{46}\) Liraglutide is generally well tolerated. The most common adverse events are gastrointestinal, i.e., nausea, vomiting and diarrhea. Hypoglycemia occurs rarely and no major hypoglycaemic events have been reported with liraglutide monotherapy (LEAD-3), liraglutide + metformin(LEAD-2) and liraglutide + metformin + rosiglitazone (LEAD-4) trial.\(^{45,47}\) In the LEAD-3 trial,\(^{47}\) which compared subcutaneous liraglutide once daily with oral glimepiride 8 mg once daily for 52 weeks in 746 subjects of type 2 diabetes, body weight fell by 2 kg and 2.5 kg
in the 1.2 mg and 1.8 mg liraglutide group respectively but increased by 1.1 kg in the glimepiride group (P< 0.001 for both liraglutide groups vs. glimepiride).

A detailed analysis of its pleiotropic or extra glycaemic effects however reveals a multifaceted character of the molecule. Liraglutide is effective in reducing body weight, decreasing visceral fat, lowering systolic blood pressure and improving lipid profile as well as other cardiovascular risk markers while reducing insulin resistance. (46,48) These beneficial effects on all components of the insulin resistance syndrome or metabolic syndrome with minimal risk of hypoglycaemia make liraglutide an attractive option for the management of insulin resistance. (45)

**Exenatide ER**

Exenatide is a synthetic form of exendin-4 which shares 53% homology with human GLP-1. (49) In June 2011, a once-weekly formulation of exenatide was approved in the EU (European Union) for the treatment of T2DM. In this extended-release formulation, exenatide is incorporated within a matrix of poly-(D,L-lactide-co-glycolide)(PLG), a polymer that degrades slowly over time when injected into the subcutaneous space, resulting in the slow release of the exenatide. (50) Compared with the twice-a-day formulation and placebo, once-weekly exenatide has been shown to produce significantly greater improvements in glycaemic control, with similar reductions in body weight and no increased risk of hypoglycaemia. (50,51)

Approval of once-weekly exenatide in the EU was granted on the basis of four Phase III clinical trials (the DURATION trials). In these trials, the safety and efficacy of once-weekly exenatide were determined in comparison with exenatide b.i.d. (DURATION-1 and DURATION-5), sitagliptin and pioglitazone (DURATION-2), or insulin glargine (DURATION-3). Exenatide and liraglutide present two distinct solutions to the same problem producing a molecule that can stimulate the GLP-1 receptor while also being resistant to DPP-4 mediated degradation. Once-daily liraglutide and once weekly extended-release exenatide (exenatide ER) are the GLP-1 receptor agonists approved at present for the treatment of T2DM. (56) In head-to-head trials of GLP-1 receptor agonists with DPP-4 inhibitors, the GLP-1 receptor agonists offer greater benefits in blood glucose reductions, weight loss and improvements in measures of beta-cell function, although gastrointestinal side effects are more common with GLP-1 receptor agonists compared with DPP-4 inhibitors. (22)

Phase III trial results demonstrate that liraglutide, exenatide BID and exenatide ER are effective at lowering blood glucose. (16) The extension studies suggest that these drugs can sustain their initial glucose lowering effects for at least 3 years, although caution should be applied to these results for selecting the patient population in extension studies. The head-to-head comparisons of the three GLP-1 receptor agonists showed that liraglutide provides better HbA1c and FPG control than exenatide BID or exenatide ER, while the greatest PPG control is conferred by exenatide BID. (56) The route of drug clearance is an important consideration in patients with renal or hepatic impairment, as these conditions can lead to the accumulation of drug compounds normally cleared via these organs. Exenatide clearance takes place predominantly via glomerular filtration, therefore it is not recommended for patients with severe renal impairment or end-stage renal disease. Both exenatide BID and exenatide ER are contraindicated in patients with severe renal impairment or end-stage renal disease (CrCl< 30 ml/min). Caution is recommended when initiating or escalating doses of exenatide in patients with moderate renal impairment and in patients with renal transplantation. (57)

Conversely, liraglutide is degraded completely within the body by DPP-4 and neutral endopeptidase. A recent study showed that mild renal impairment had no effect on the safety and efficacy of liraglutide. (57) However, owing to limited therapeutic experience, liraglutide is not recommended for use in patients with moderate or severe renal impairment or end-stage renal disease. (58) As exenatide is primarily excreted via the kidney, hepatic dysfunction is not expected to affect blood concentrations of exenatide BID or exenatide ER and no dose adjustment is recommended. (57)

**Lixisenatide**

Lixisenatide is a GLP-1 receptor agonist structurally based on exenatide with a modified C terminus of six Lysine residues that can withstand physiological degradation by DPP-4 and therefore, prolong the physiological effects of GLP-1 itself. In a Phase III trial, (59) 542 patients received metformin plus lixisenatide 5, 10, 20 or 30 μg once or twice daily or placebo. Lixisenatide significantly improved mean HbA1c in a dose-dependent manner with all doses versus placebo (p < 0.01). Dose-dependent improvements were also observed for fasting blood glucose levels.

As in the Phase II studies, significant reductions in body weight were reported with lixisenatide 20 and 30 μg once daily and 30 μg twice daily doses compared with the placebo (p < 0.01). The most frequent adverse event reported was nausea. Lixisenatide is undergoing further evaluation in combination with other antidiabetic agents and as monotherapy in the Phase III Get Goal clinical trial program. Of particular note, further to successful outcomes from the GETGOAL-L-ASIA study, (60) lixisenatide is being evaluated in combination with insulin glargine in a Phase III study.

**Albiglutide**

Albiglutide is a GLP-1 dimer albumin fusion peptide, which has a prolonged half-life as a result of its fusion with albumin...
and associated resistance to DPP-4, leading to prolonged physiological effects of GLP-1 itself. Due to this long half-life, albiglutide can be administered once weekly via s.c. injection.\(^{61,62}\) Data from early phase trials suggested that albiglutide significantly reduced HbA1c levels compared with placebo. Its use was associated with weight loss in obese individuals and was well tolerated compared with exenatide.\(^{61,62}\)

In a large, randomized, placebo controlled 16-week trial in 356 patients, albiglutide was compared in various doses and regimens against exenatide, albiglutide 4, 15 or 30 mg weekly or 100 mg monthly. Compared with placebo, mean HbA1c was significantly reduced by 0.87 ± 0.65 and 0.87 ± 0.87 from baseline by albiglutide 30 mg weekly and 100 mg monthly respectively (each p < 0.05 vs. placebo). Similarly, fasting plasma glucose levels for the above dosing regimens were significantly lower than placebo (p < 0.05). Weight loss of between 1.1 and 1.7 kg was also observed with the above two doses with no significant adverse effects. As of now, Phase III trials with albiglutide are currently ongoing.\(^{63,64}\)

**Taspoglutide**

Taspoglutide is another long-acting GLP-1 receptor agonist. It has 97% homology with human GLP-1 and is similar in structure to native GLP-1 except that it has two amino acid substitutions in positions 8 and 35 with amino isobutyric acid, which render the molecule resistant to degradation by DPP-4. Taspoglutide is administered once weekly s.c., but has also been shown to be effective when given every 2 weeks.\(^{65}\)

In an early phase trial,\(^{66}\) 48 patients were randomized to a single s.c. injection of taspoglutide (1, 8 or 30 mg) or placebo and followed for 14 days. Compared with placebo, the 8 mg and 30 mg doses of taspoglutide significantly reduced glycaemic parameters, which lasted for up to 14 days with the 30 mg dose (p < 0.001). The most common adverse events were primarily gastrointestinal in nature, dose-dependent and transient. In a larger 8 week trial in 306 patients, greater reductions from baseline in HbA1c were observed in all taspoglutide groups compared with placebo after 8 weeks of treatment (p < 0.0001).\(^{67}\) Compared with placebo, bodyweight loss was significantly greater in the 10 mg (p < 0.0035) and 20 mg (p < 0.0001) once weekly groups and in the 20 mg every 2 weeks group (p < 0.0083). The most common adverse event was nausea and the incidence of hypoglycaemia was very low.

Ratner and co-workers\(^{68}\) evaluated the safety and tolerability of high doses of taspoglutide. Patients were randomized to placebo or taspoglutide (20 mg, three separate groups) administered once weekly s.c. for 4 weeks. This was followed by dose maintenance at 20 mg or titration to 30 or 40 mg once weekly with a matched placebo for an additional 4 weeks. Taspoglutide was well tolerated at the high doses and successfully lowered HbA1c in all treated arms. Furthermore, up-titration of dose was not associated with a worsening adverse event profile. Indeed, in various clinical trials, taspoglutide has been shown to significantly reduce three of five diagnostic criteria for metabolic syndrome, namely fasting blood glucose, waist circumference and fasting triglyceride. As of now, Taspoglutide is undergoing Phase III clinical trials as monotherapy and in combination with insulin glargine, or metformin and/or pioglitazone.\(^{65}\)

**Semaglutide**

Oral semaglutide is the first FDA-approved glucagon-like peptide-1 receptor agonist. Oral semaglutide is an option for type 2 diabetes patients who need glucose control, weight loss and want to avoid injections.\(^{69}\)

Semaglutide acts like human glucagon-like peptide-1 (GLP-1) so that it increases insulin secretion, thereby increasing sugar metabolism. It is distributed as a metered subcutaneous injection in a prefilled pen. One of its advantages over other anti-diabetic drugs is that it has a long duration of action, thus only once-a-week injection is sufficient.

An injection version (Ozempic) was approved for medical use in the United States in December 2017 and in the European Union, Canada, and Japan in 2018. A version that is taken by mouth (Rybelsus) was approved for medical use in the United States in September 2019 and in the European Union in April 2020. It is the first glucagon-like peptide (GLP-1) receptor protein treatment approved for use in the United States that does not need to be injected. It was developed by Novo Nordisk.\(^{69}\)

It increases the production of insulin, a hormone that lowers the blood sugar level. It also appears to enhance the growth of \(\beta\) cells in the pancreas, which are the sites of insulin production. On the other hand, it inhibits glucagon, which increases blood sugar. It additionally reduces food intake by lowering appetite and slows down digestion in the stomach. In this way, it works in body fat reduction.

Semaglutide is superior to placebo and sitagliptin, exenatide extended-release, dulaglutide and insulin glargine for reduction of glycated hemoglobin levels and weight. Semaglutide can be considered a preferred first injectable option in the management of type 2 diabetes.

The additional possible benefit of CV risk reduction in patients with established CVD makes it an excellent option for these high-risk patients.\(^{69}\)

**Conclusion**

Diabetes mellitus is a serious and growing issue for health care practitioners worldwide and for many patients as the condition is currently insufficiently managed. GLP-1 is an attractive therapeutic target for the treatment of T2DM because of its wide ranging effects such as potentiation of insulin secretion, inhibition of glucagon secretion, suppression of appetite and

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food intake. These agents can be combined with oral antidiabetic agents or used as monotherapy. Exenatide was the first approved GLP-1 receptor agonist. Although it is effective and used widely, its twice-daily dosing can be inconvenient, which has led to the development of longer-acting GLP-1 receptor agonists. Liraglutide was approved for the treatment of T2DM in 2010 and it has a more convenient once-daily dosing schedule. Other GLP-1 receptor agonists with longer durations of action are in development and have shown promising results in early-phase trial, some of which have once weekly or even less frequent dosing regimens. Semaglutide is a welcome addition to the anti-hyperglycaemic agent armamentarium in type 2 diabetes, offering robust A1C lowering and weight loss across a variety of background therapies, as well as CV safety and convenient once-weekly dosing, and it may have a possible CV benefit in those with established CVD. Furthermore, more and long term studies are required to establish the clinical use of these newer GLP-1 analogues in the management of metabolic syndrome and obesity.

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