Glucagon-like peptide-1 and glucagon-like peptide-1 receptor agonists in the treatment of type 2 diabetes

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Introduction

A total of 387 million people worldwide have been diagnosed with diabetes, of which approximately 95% have type 2 diabetes (T2D). Patients with T2D suffer from a number of diabetes-related complications such as cardiovascular disease, neuropathy, nephropathy, and other organ disturbances. Although the American Diabetes Association recommends metformin treatment as a first-line therapy, metformin treatment alone is insufficient to achieve target blood glucose level in most patients. Currently, diabetes medications are recommended on a patient-specific basis by considering adverse drug reactions. Several classes of therapy can be used as add-on medications. Based on these findings, many scientists and physicians have developed alternative medications. Among them, glucagon-like peptide-1 (GLP-1) receptor agonists are innovative treatments for T2D. These agonists are beneficial for blood glucose control, pancreatic β-cell function, and other diabetes-related conditions. Recently the frequency of GLP-1 receptor (GLP-1R) agonist based therapy has been increased, particularly in the United States, Europe, and several other nations. Since GLP-1R agonists differ with respect to clinical efficacy, tolerability, administration requirements, and dosing frequency, each medication potentially provides unique advantages and disadvantages. The purpose of this article is to summarize current information regarding U.S. Food and Drug Administration (FDA)-approved GLP-1R receptor agonists, with a particular focus on efficacy and clinical studies. Finally, we discuss the potential benefits of these agonists in the treatment of T2D.

Glucagon-like peptide-1

GLP-1 is the transcription product of a pro-glucagon gene. Absorbed nutrients in the small
intestine induce GLP-1 secretion from L cells in the intestinal ileum. GLP-1 exerts several effects that are relevant to the treatment of diabetes mellitus. First, GLP-1 increases glucose transporter 2 expression in pancreatic β cells; this molecule plays a role in glucose movement across the cell membrane. Second, GLP-1 induces pancreatic β cells to secret insulin in response to increased glucose contents, while also restricting glucagon release from pancreatic a cells. Third, GLP-1 reduces the secretion of proinflammatory cytokines such as interleukin-6, tumor necrosis factor-α, and interferon-γ. Therefore, GLP-1 restores pancreatic β-cell mass and insulin sensitivity. The action of GLP-1 on the proliferation of β cell and antiapoptosis is observed in the experimental animal model, but still not confirmed in the clinical cases. Finally, the postprandial GLP-1 response is decreased in T2D. This impairment alone could contribute to the pathogenesis of diabetes. However, although GLP-1 secretion is reduced in T2D, patients with T2D who receive GLP-1 infusions exhibit increased insulin release and improved glucose tolerance. These properties of GLP-1 make it an interesting potential therapeutic agent for T2D.

1. Structural features of GLP-1 and the GLP-1R

GLP-1 is a member of the glucagon peptide family and is derived from the preproglucagon gene expression located on chromosome 17. Proprotein convertase (PC) is an important enzyme that activates the product of the pro-glucagon gene by cleaving a peptide at the C-terminal domain, thereby enabling the biological activity of this peptide. Specifically, prohormone convertase 1/3 (PC1/3) generates GLP-1 in intestinal L cells. The GLP-1 peptide is composed of 30 amino acids and undergoes amination of the C-terminal domain. This amination on His7 is required for the enzymatic activities of GLP-1, such as its insulinotropic and glucagon-inhibiting activities. Also, amination extends the survival time of GLP-1. GLP-1 exists in 2 forms, the GLP-1 (7-36) amide form (which accounts for 80% of all circulating GLP-1) and the GLP-1 (7-37) form, which harbors an additional Gly residue (Gly37) compared to the GLP1 (7-36) amide form. These 2 forms result from tissue-specific differences in posttranslational processing of the preproglucagon gene product. Generally, the GLP-1 (7-36) amide form is secreted in pancreatic tissue, while GLP-1 (7-37) is secreted in the hypothalamus and intestinal ileum. The central domain of GLP-1 has an alpha-helical structure, while the N-terminal domain forms a coil structure. Also, the hydrophobic amino acids Phe6 and Val10 and the short chain polar amino acid Thr7 form a helix N-terminus-capping motif through hydrogen bonding and hydrophobic interaction. This capping motif introduces a specific local fold that facilitates receptor activation for peptide-receptor binding.

GLP-1 mediates its physiological effects by interacting with members of the guanine nucleotide binding protein (G-protein) coupled receptor family. The GLP-1R is composed of 463 amino acids and has eight hydrophobic domains. GLP-1 and GLP-1R have important affinity domains determined by ligand selectivity. Extracellular N-terminal hydrophobic domains, tryptophan residues, alanine residues, and cysteine residues are critical for the interaction between GLP-1 and GLP-1R. In particular, His7 (in the N-terminus of GLP-1) has a free alpha-amino group and an imidazole side chain that are important for the GLP-1R/SLP-1 interaction. In addition, denaturation, isolation, and elimination of the GLP-1R N-terminal domain result in loss of affinity for the peptide. Furthermore, residues Tyr149, Met204, and Tyr205 are required for the biological activity of GLP-1; GLP-1 exerts this activity through the cAMP-dependent pathway.

2. Physiological properties of GLP-1

The glucose-dependent insulinotropic reaction is decreased or absent in patients with T2D. Pharmacological applications for GLP-1 in patients with T2D have been intensely investigated. When only blood glucose level is highly maintained, GLP-1 increases insulin secretion from pancreatic β-cells while suppressing glucagon secretion from pancreatic α-cells. In addition, GLP-1 controls pancreatic β-cell proliferation and apoptosis. Furthermore, GLP-1 controls gastric emptying, motility, colonic transit time, satiety action, energy expenditure, and thermogenesis. Cumulatively, these studies have
indicated that GLP-1 is one of potential new drugs for patients with T2D (Fig. 1).

1) Intestine

GLP-1 affects various gastrointestinal functions such as gastric emptying, motility, and colonic transit time. Interactions between brain and GLP-1 are associated with the inhibition of gastric emptying via the nonadrenergic and noncholinergic pathways. GLP-1R is highly expressed in myenteric neurons and submucosal neurons of the duodenum and proximal colon. When GLP-1R is activated in enteric neurons, GLP-1 mediates changes in gastrointestinal function. In addition, GLP-1 stimulates innervation to the intestinal circular muscle layer by cholineric neuron reactions. These reactions are associated with peristalsis because intestinal circular muscle layer contraction is dominant in this process. In addition, GLP-1 extends colonic transit time by central neuronal actions and acts on the dorsal motor nucleus of the vagus nerve to mediate changes in parasympathetic neural input. This reaction enhances cholineric stimulation and affects colon motor contraction, thereby influencing colonic transit time.

Central nervous GLP-1 is important for controlling the satiety actions of central and peripheral nerves. In enteric or vagal neurons, GLP-1 activates brain circuits that affect food intake by inducing c-Fos expression in the hypothalamus paraventricular nucleus (PVN). In addition, leptin receptors are highly expressed in the mediobasal hypothalamic nucleus (MBH), which is the main site of GLP-1 action. These findings suggest that central endogenous GLP-1 produced in the NTS might act on GLP-1R in the same nuclei, and that these feedback loops are associated with satiety roles.

2) Brain

In the brain, GLP-1 is produced by noncatecholaminergic neurons of the nucleus of solitary tract (NTS). These neuron stretches throughout areas in the hindbrain and hypothalamus such as the PVN, the dorsal medial nucleus of the hypothalamus, and the arcuate nucleus (ARC). Moreover, gut-derived GLP-1 interacts with the brain by GLP-1R expressed in innervating fiber neurons, where the blood-brain barrier has enhanced permeability.

In one study that aimed to identify the specific neuronal site affected by GLP-1R agonist interaction with GLP-1R, the gene encoding GLP-1R in the central nervous system (CNS) or peripheral nervous system was deleted. That study found that the loss of GLP-1R in the CNS did not affect the regulation of food uptake or body weight, while peripheral nervous system GLP-1R reduction was associated with decreased food uptake and weight loss. This result demonstrates that the peripheral nervous system is essential for complete anorectic response and weight loss effects. Another study was conducted to identify the peripheral neuronal mechanism associated with the effects of GLP-1R on food uptake and weight loss. In that study, GLP-1R antagonist was injected into nerves in specific regions or into nuclei in an ex vivo electrophysiological study. Also, fluorescent-labeled GLP-1R antagonists were peripherally administered in a rat model. That study found that the ARC was responsible for controlling appetite and weight loss. Specifically, neuropeptide Y/agouti-related protein (NPY/AgRP) neurons control appetite by the orexigenic effect, and pro-opiomelanocortin/cocaine-and amphetamine-regulated transcript (POMC/CART) neurons are sensitive to peripheral hormones such as insulin and leptin by anorexigenic effects.

Aside from these examples, no uptake of peripherally administered GLP-1R agonist was found in the NTS. In addition, a GLP-1R agonist was shown to act indirectly through gamma-Aminobutyric acid neurons to inhibit NPY/AgRP neurons in the ARC.

3) Pancreas

GLP-1R is highly expressed on the pancreatic β-cell membrane. In the presence of high concentrations of glucose, GLP-1 interacts with GLP-1R, resulting in cyclin AMP (cAMP) formation. The subsequent increase in cAMP leads to the activation of cAMP-regulated guanine nucleotide exchange factor 2 (cAMP-GEFII or Epac2) and protein kinase A (PKA). Epac2 and PKA regulate ion channel activity, specifically by closing β-cell ATP sensitive potassium channels. As a result, the membrane potential changes, and the pancreatic β cells are sensitized to glucose. In addition, Epac-2 is associated with a critical step in signaling pathways such as those containing Ras superfamily guanine nucleotide exchange factor binding proteins. Epac-2 is also associated with Ca^2+ release from the endoplasmic reticulum, resulting in exocytosis of insulin-containing vesicles. Also, PKA is associated with phosphorylation reactions important for insulin secretion from pancreatic β cells. GLP-1 also regulates the expression of specific genes in pancreatic β cells. First, increased intracellular Ca^2+ concentration affects the level of insulin gene transcription. As a result, intracellular insulin contents are increased, thereby elevating the insulin contents of β cells. Secondly, GLP-1 activates pancreatic duodenal homeobox-1 (PDX-1), which is associated with insulin gene transcription. Additionally, PDX-1 is a critical factor for promoting β-cell proliferation, differentiation, and survival. Moreover, GLP-1 promotes glucose-dependent insulin secretion when the intracellular insulin contents of pancreatic β cells increase. Furthermore, GLP-1 increases the expression of glucose transporter genes and glucokinase, which are associated with glucose transport and metabolism. GLP-1 also prevents pancreatic β-cell apoptosis by controlling the expression of bcl-2 (antiapoptotic protein) and caspase-3 (pro-apoptotic protein). In vitro studies of the effects of GLP-1 on pancreatic β cells, GLP-1-treated human islets showed increased level of bcl-2 protein and decreased level of caspase-3 protein. Also, GLP-1-treated islets had more normal morphology compared to untreated islets.

Recent studies have demonstrated that GLP-1 also affects pancreatic a cells by improving abnormalities in α-cell glucose sensing. These studies have found that, when given before a
meal, GLP-1 decreases prandial glucose release and inhibits inappropriate meal-induced glucagon release. Another study compared the effects of GLP-1 on patients with T2D versus nondiabetic subjects and found that glucose-infused patients with diabetes showed transient increase in glucagon level and failed to suppress hyperglycemia conditions. Moreover, subsequent GLP-1 infusion during hyperglycemia led to decreased plasma glucagon level in patients with T2D compared to those of nondiabetic subjects. In a long-term study of GLP-1-based therapy in T2D, continuous infusion of GLP-1 tended to lower glucagon level and to substantially reduce blood glucose level.

4) Adipose tissue
The relationships between brown adipose tissue (BAT) thermogenesis and white adipose tissue (WAT) browning with GLP-1 action are largely unknown, but recent studies have attempted to answer this difficult question. For instance, GLP-1 was recently found to regulate BAT thermogenesis without causing any diet changes. Also, many genes associated with the thermogenic program are highly expressed in the brain, such as uncoupling protein-1 (UCP-1) and peroxisome proliferator activated receptor gamma co-activator-1 alpha. In contrast, a GLP-1 receptor knock-out mouse did not show any change in BAT thermogenesis or expression of genes involved in the thermogenic program. Also, central injection of GLP-1R agonists resulted in electrophysiological activity of sympathetic fibers. These results indicate that interaction between the brain and BAT is associated with the sympathetic nervous system. Furthermore, central injection of GLP-1R agonists resulted in WAT browning. It is well known that many neurons in the CNS express GLP-1R, especially ventromedial nucleus (VMH) neurons in the hypothalamic nuclei, an area critical for energy balance. VMH neurons modulate sympathetic nervous systems such as the raphe pallidus and inferior olive systems. These 2 sympathetic nervous systems are associated with regulation of BAT thermogenesis. Furthermore, a VMH knockout mouse showed lower energy expenditure and UCP-1 expression in BAT. In addition, gene modulation studies have demonstrated the effect of VMH in BAT thermoregulation. Specifically, in the VMH knockout mouse, steroidogenic factor-1 neurons showed lower energy expenditure and decreased amount of UCP-1 in the BAT. AMP-activated protein kinase in the VMH sympathetically regulates thyroid hormone and estradiol, thereby affecting thermogenesis by BAT.

A few studies have demonstrated the central control of WAT browning. In one study, brain SIRT-1 (NAD-dependent deacetylase sirtuin-1) was determined to play a critical role in WAT browning. Moreover, SIRT-1 knockout POMC neurons were shown to exhibit reduced sympathetic nerve activity, UCP-1 expression, and brown fat-like activity in perigonadal WAT. Another study also suggested that AgRP neurons within the ARC inhibit the WAT browning effect.

Limitations of GLP-1 in the treatment of T2D
Native GLP-1 has a very short half-life (about 2 minutes) because of rapid degradation by the endogenous enzymes dipeptidyl-peptidase-IV (DPP-4) and neutral endopeptidase (NEP). DPP-4 is an exopeptidase that is highly concentrated in hepatocytes, intestinal brush-border membranes, the kidney, the capillary endothelium, and plasma. This enzyme cleaves peptide bonds and ultimately releases a single amino acid or dipeptide from the native peptide chain. Native GLP-1 is cleaved by DPP-4 directly after 7His and 8Ala, 2 N-terminal amino acids. The cleaved fragment (9-36) does not exert insulinotropic effects. Also, native GLP-1 is degraded by neutral endopeptidase 24.11 (NEP 24.11), also known as neprilysin. This enzyme is a zinc-dependent metalloproteinase that is expressed in many different tissues, with especially high expression level in the kidney. NEP 24.11 cleaves a hydrophobic residue or the N-terminal side of aromatic residues from native peptides. The modified GLP-1 fragment undergoes rapid renal clearance. Therefore, it is necessary to develop modified versions of GLP-1 or to synthesize GLP-1R agonists to achieve better bioavailability and clinical efficacy in the treatment of patients with T2D.

Pharmacokinetics of FDA-approved GLP-1R agonists
Synthetic GLP-1R agonists are resistant to degradation by DPP-4 and consequently exhibit extended bioavailability, thereby improving their clinical efficacy. These agonists bind to

Fig. 2. Amino acid sequence of glucagon like peptide-1 (GLP-1) and GLP-1 receptor agonists, exenatide, liraglutide, albiglutide and dulaglutide. Modified amino acids are highlighted in red.
GLP-1R and stimulate its pharmacological effects, increasing glucose-dependent insulin release from pancreatic β cells, suppressing the release of glucagon from pancreatic α cells, delaying the rate of gastric emptying, and slowing the glucose absorption rate. Several FDA-approved GLP-1R agonists are available for use in the United States and the European Union (Fig. 2). Since the molecular structure, pharmacokinetics, efficacy, administration requirements, and tolerability may differ between GLP-1R agonists, each agonist offers specific advantages and disadvantages. Consequently, each agonist should be assessed independently, and therapeutic regimens should be customized to individual patients.

1. Exenatide

The first GLP-1R agonist to be approved was Exenatide (marketed as Byetta), which was approved by the FDA in 2005. Exenatide is a synthetic form of exendin-4, which is a hormone found in gila monster saliva that is composed of 39 amino acid peptides and shares 53% sequence homology with GLP-1[72], making it a potent GLP-1R agonist. Exenatide is also resistant to degradation by DPP-4 because it has Gly8 in the place of Ala8, the residue on which DPP-4 acts. Furthermore, there are no target sites for NEP 24.11[73] in exenatide, the longer C-terminus of which may be responsible for its prolonged half-life (about 2–4 hours in humans[74]). Like GLP-1, exenatide binds to GLP-1R and has several antihyperglycemic effects, such as increasing glucose-dependent insulin release and decreasing glucagon level[75,76].

Exenatide has been used as a monotherapy or in combination with insulin or oral agents. Because exenatide restores the normal first-phase insulin release that is lost in people with diabetes, it should be injected before meals to successfully suppress hepatic glucose production[77]. Exenatide must be injected subcutaneously (abdomen, thigh, or upper arm) twice daily prior to eating meals; to minimize the risk of hypoglycemia, injections should be administered at intervals of at least 6 hours. At the beginning of treatment, patients should be injected with 5-μg doses to increase drug tolerability. Since exenatide has dose-dependent effects[78], after 1 month of drug administration, patients should be injected with 10-μg doses[79]. If the patients become noncompliant with the 10-μg doses due to side effects such as nausea or vomiting, a 5-μg dose has also been shown to lower overall glycosylated hemoglobin (HbA1c) concentration[80].

Another long-acting exenatide, Bydureon, is administrated once weekly. This therapeutic was introduced in the United States in 2012. Bydureon has the same pharmacological compound, exenatide, and is given twice daily. Specifically, Bydureon consists of a poly-microsphere drug carrier that releases exenatide into the blood for 10 days, resulting in sustained drug release and longer lasting effects. Bydureon is administered once weekly in 2-mg doses through the subcutaneous route[81].

2. Exenatide in clinical trials

The efficacy of twice-daily exenatide treatment of patients with T2D has been evaluated in multiple phase 3 clinical studies. One such study was entitled “AC2993: Diabetes Management for Improving Glucose Outcomes (AMIGO).” The AMIGO-1 study was a 30-week study that assessed the clinical efficacy of twice-daily exenatide to ameliorate glycemic control in patients with T2D who were already receiving metformin therapy. Patients already receiving 1.500 mg of once-daily metformin were randomized to receive placebo, twice-daily exenatide (5 μg) for the entire study period, or twice-daily exenatide (5 μg) for the first 4 weeks, after which the dose was changed to 10 μg twice daily. At the termination of the study, patients who were treated with 10-μg twice-daily exenatide exhibited reduction of HbA1c level by about 0.78%, while the 5-μg twice-daily groups achieved approximately 0.4% reduction. These reductions were statistically significant compared with placebo values (P<0.002). Also, participants who were given either dose of exenatide (5 or 10 μg) experienced significant dose-dependent weight loss. However, adverse symptoms such as nausea, vomiting, and hypoglycemia were frequently observed with exenatide treatment. These results indicate that exenatide treatment for T2D can yield an additive effect in patients unable to achieve appropriate glycemic control with metformin therapy[77].

Twice-daily exenatide was demonstrated to yield superior glycemic control compared with a dipeptidyl peptidase inhibitor (sitagliptin)[82]. In one clinical trial, participants already taking metformin received a 100-μg dose of sitagliptin daily for 2 weeks or a 5-μg dose of exenatide twice a day for 1 week. The latter dose was titrated to 10 μg of exenatide twice daily for 1 week. At the study’s conclusion, participants who received exenatide treatment exhibited significantly reduced postprandial glucose level. Furthermore, the exenatide treatment group showed significantly increased insulin secretion and decreased postprandial glucagon secretion. Although the duration of this trial was relatively short, it demonstrated that GLP-1R agonists enable superior glycemic control compared to DPP-4 inhibitors[83].

The clinical efficacy of once-weekly exenatide was examined in multiple phase 3 studies, including the DURATION program (Diabetes Therapy Utilization: Researching changes in A1C, Weight and Other Factors Through Intervention with Exenatide Once Weekly). The DURATION trials estimated the efficacy and safety of a 2-mg dose of exenatide once weekly in patients with T2D[84] and compared them to those of several another treatments such as twice-daily exenatide, insulin glargine, liraglutide, and other medications[1,5,79,80]. In one clinical trial, a once-weekly 2-mg dose of exenatide was compared with a twice-daily 10-μg dose of exenatide. The duration of this trial was 30 weeks, and participants were given metformin as a background treatment. At the termination of the study, participants exhibited significantly reduced HbA1c level (approximately 1.9% compared with 1.5% reduction with twice-
daily exenatide \( (P=0.0023) \). Moreover, 77% of participants achieved a target HbA1c level when treated with once-weekly exenatide compared with 61% of twice-daily exenatide group \( (P=0.0039) \). Furthermore, the once-weekly exenatide group experienced significantly reduced fasting and postprandial glucose level. Since the poly-microsphere form of once-weekly exenatide results in more sustained drug-release compared with the daytime drug-release of twice-daily exenatide\(^8\), the fasting glucose level was more highly decreased in the once-weekly exenatide group and the postprandial glucose level was greatly reduced with the twice-daily form\(^9\). Regarding adverse effects, more participants receiving once-weekly exenatide experienced injection site pruritus, while treatment-related nausea and vomiting were more frequent in the twice-daily exenatide group. Cumulatively, the data from this trial indicate that once-weekly exenatide is superior for achieving target HbA1c level and blood glucose level without increasing the rate of hypoglycemia\(^9\).

In the DURATION-6 trial, the clinical efficacy of once-weekly exenatide was evaluated and compared to that of liraglutide, an FDA-approved GLP-1R agonist\(^7\). While participants continued background medications such as metformin, they were randomized to receive a 2-mg dose of exenatide once weekly or a 1.8-mg dose of daily liraglutide. At the conclusion of the study, the exenatide-treated group exhibited a significant reduction of HbA1c (about 1.28%), while the liraglutide-treated group showed a 1.48% reduction \( (P=0.02) \)\(^7\). All participants experienced treatment-dependent weight loss; liraglutide-treated patients exhibited greater weight loss\(^7\), although patients receiving once-weekly exenatide maintained this weight loss for a longer duration\(^7\). Also, liraglutide-treated patients experienced a significant reduction in fasting blood glucose level compared with once-weekly exenatide-treated patients \( (P=0.02) \). However, some of the liraglutide-treated patients displayed adverse symptoms such as nausea, and more patients quit liraglutide therapy because of severe adverse effects\(^7\).

In the DURATION-3 trial, the clinical efficacy of once-weekly exenatide was estimated and compared to that of insulin glargine for 26 weeks. Participants were randomized to receive a 2-mg dose of weekly exenatide or an initial dose of 10 units of daily insulin glargine with background metformin therapy, with or without sulfonylurea. If the participant experienced treatment-dependent hypoglycemia, the sulfonylurea dose was reduced. At the conclusion of the study, the once-weekly exenatide-treated group exhibited significantly reduced HbA1c level (about 1.5%) \( (P=0.017) \) compared with the insulin glargine-treated group (1.3%)\(^6\). Furthermore, because of the effects of the GLP-1R agonists on caloric intake, satiety, and postprandial glucose concentrations\(^8\), once-weekly exenatide-treated patients experienced greater reductions in postprandial glucose concentration\(^6\). Also, exenatide-treated patients experienced greater weight loss compared with the treatment-dependent weight gain of insulin therapy (about 1.4 kg). With respect to adverse symptoms, once-weekly exenatide-treated patients experienced higher rates of adverse effects such as nausea and vomiting. However, hypoglycemia occurred more frequently with insulin glargine treatment, especially with background sulfonylurea therapy\(^6\).

The trials above indicate that once-weekly exenatide should be given to patients with other medications for a few weeks to ensure that optimum glycemic control is achieved, since the steady state concentrations of once-weekly exenatide are reached within 1 week\(^6\).

3. Liraglutide

Liraglutide (Victoza) was introduced in the United States in 2010 as a second GLP-1R agonist. This protein has 97% sequence homology with native GLP-1\(^1\) and exhibits a prolonged half-life of 13 hours. The long half-life is achieved by peptide acylation with a fatty acid at Lys26 via a glutamoyl spacer, forming a lipophilic micelle-like structure\(^3\). Acylated liraglutide adheres to albumin and self-associates after subcutaneous injection. This phenomenon allows the slow release from albumin, delayed degradation, and reduced renal clearance of liraglutide compared to GLP-1\(^1\). Liraglutide exerts a number of effects similar to those exerted by GLP-1. For instance, liraglutide attenuates β-cell apoptosis and stimulates glucose-dependent insulin secretion from pancreatic β cells. Furthermore, compared to exenatide, liraglutide is more efficient in decreasing HbA1c because of its longer half-life\(^6\).

Liraglutide, which is administered using prefilled pens, has been used as monotherapy as an adjunct to exercise and diet or in combination with basal insulin and oral agents in patients with T2D. Liraglutide is not considered a first line therapy. Initially, liraglutide should be given to patients at a dose of 0.6 mg once daily for 1 week to increase drug tolerability. The dose should then be adjusted to 1.2 mg per day. If the glycemic goals are not achieved, the dose can be increased to 1.8 mg per day\(^3\).

4. Liraglutide in clinical trials

The clinical efficacy of once-daily liraglutide in patients with T2D was demonstrated in a study series entitled ‘LEAD (Liraglutide Effect and Action in Diabetes)’. In the LEAD-6 clinical study, which lasted for 26 weeks, the efficacy of liraglutide with background metformin and/or sulfonylurea therapy was compared with that of twice-daily exenatide\(^6\). Participants with HbA1c level ranging from 7%–11% were randomized to receive daily liraglutide (1.8 mg) after a titration period of once-weekly liraglutide (0.6 mg), once-weekly (1.2 mg) for 2 weeks, or 5 μg of exenatide twice daily for 4 weeks. The latter dose was titrated to 10 μg twice daily. At the conclusion of this trial, the liraglutide-treated group exhibited a significant reduction in HbA1c level by about 1.12% compared to the exenatide group, which had 0.79% reduction. Also, 54% of the participants in the liraglutide therapy group achieved the target HbA1c level, compared to more than 43% of the participants in the exenatide-treated group. With respect to reducing blood glucose level, liraglutide was superior for the fasting state, while
exenatide was better for the postprandial state (P<0.0001). Both groups showed similar weight loss (approximately 3 kg). Adverse effects such as nausea occurred in both groups at similar rates. However, the liraglutide-treated group showed rapid recovery from symptoms within 6 weeks, while the exenatide-treated group required 22 weeks.

In the LEAD-5 trial, liraglutide was compared with insulin glargine in patients with background metformin and/or sulfonylurea therapies. Participants were randomized to receive once-daily liraglutide (1.8 mg) after a 2-week titration time or insulin glargine. At the conclusion of the 26-week study, the liraglutide-treated group exhibited significantly reduced HbA1c level (approximately 1.33% reduction), while the insulin-treated group exhibited a 1.01% reduction in HbA1c level. Also, the liraglutide-treated group experienced weight loss and mild to moderate gastrointestinal symptoms such as mainly nausea (14%), diarrhea and vomiting, while the insulin-therapy group gained weight. The rates of hypoglycemia were similar between the 2 groups. This study demonstrated that liraglutide has clinical efficacy for reducing HbA1c level and body weight in patients with T2D, without causing severe side effects.

5. Albiglutide (Tanzeum)

In 2014, the FDA approved albiglutide (Tanzeum), a GLP-1R agonist, as an adjunct to exercise and diet for improving glycemic control in T2D. Albiglutide increases glucose-dependent insulin secretion, slows gastric emptying, and decreases food uptake. Furthermore, albiglutide has a prolonged half-life (about 5 days) due to the replacement of two amino acids (alanines) with glycines, thereby allowing albiglutide to bind albumin in vivo.

Similar to other GLP-1R agonists, albiglutide is not considered a first-line agent. Albiglutide is given as a 30-mg dose once a week by subcutaneous injection (abdomen, upper arm, or thigh) or by pens prefilled with a powder; doses are administered regardless of meal timing. Following initial administration, therapeutic concentrations of albiglutide can be achieved within 5 days. Steady state concentrations are maintained by 28–35 days after the initial injection. For patients who cannot achieve appropriate glycemic control with 30-mg albiglutide, the dose can be increased to 50 mg once weekly, which has been shown to result in improved glycemic control.

6. Albiglutide in clinical trials

The clinical trials of albiglutide comparing with that of insulin glargine in patients with T2D were conducted in a study series entitled HARMONY. In the HARMONY-2 (efficacy and safety of once-weekly GLP-1 receptor agonist albiglutide) clinical study, patients were randomized to receive either once-weekly albiglutide (30 mg, titrated up to 50 mg if required for glycemic control) or 10 units of insulin glargine once daily. At the end of the treatment period, HbA1c level had decreased (by about 0.66%) in the albiglutide group, while that in the insulin glargine group had decreased by 0.81%. This study demonstrates the noninferiority of albiglutide treatment with respect to glycemic control. Furthermore, the insulin-treated group exhibited treatment-related weight gain, while albiglutide confers additional benefits such as weight loss.

In the HARMONY-3 clinical trials (104-week randomized, double-blind, placebo- and active-controlled trial assessing the efficacy and safety of albiglutide compared with placebo, sitagliptin, and glimepiride in patients with T2D taking metformin), the efficacy of albiglutide was examined in patients with T2D which was not controlled by metformin alone therapy. Participants (average HbA1c level of 8.3%) were randomized to receive albiglutide or a DPP-4 inhibitor (sitagliptin) based on presence of metformin therapy. In participants who received albiglutide, HbA1c and fasting blood glucose levels were significantly reduced compared with those in sitagliptin-treated participants. Of particular note, albiglutide is noninferior to insulin glargine and inferior to sitagliptin. In the HARMONY-7 trial (once-weekly albiglutide versus once-daily liraglutide in patients with T2D inadequately controlled on oral drugs), participants were randomized to receive either a 30-mg dose of albiglutide once weekly, titrated to a 50-mg dose once weekly after 6 weeks, or a 0.6 mg daily dose of liraglutide, titrated to 1.8 mg after 2 weeks. At the conclusion of the 32 weeks trial, 52% of the liraglutide-treated participants had reached their HbA1c level under 7% while 42% of albiglutide-treated groups had achieved. Noninferiority of albiglutide could not be demonstrated in head-to-head trials with liraglutide. Also, weight loss and gastrointestinal side effects were not as frequent compared to those in patients receiving liraglutide. However, adverse symptoms such as nausea, vomiting, and hypoglycemia were more frequent with liraglutide therapy. These clinical trials indicate that albiglutide therapy yield better results for patients who experience intolerable adverse symptoms in response to short-acting GLP-1R agents.

7. Dulaglutide (GLP-1Fc, Trulicity; LY2189265)

Dulaglutide (Trulicity) received FDA approval in 2014 as a long-acting human GLP-1R agonist and is given as an adjunct to diet and exercise for T2D. Dulaglutide consists of 2 disulfide-linked chains that contain a sequence analogous to GLP-1. Specifically, the sequence is approximately 90% homologous to that of native GLP-1. These chains are covalently linked to a modified immunoglobulin G4 heavy chain fragment (IgG4-Fc) by a small peptide linker. The modified IgG4-Fc domain of the molecule reduces its immunologic cytotoxicity by suppressing Fc receptor affinity potential. Also, this structure optimizes the clinical effects of dulaglutide by protecting it from DPP-4-mediated degradation.

Furthermore, the increased molecule size resulting from IgG4-Fc linkage reduces the elimination rate. Due to these features, dulaglutide has a significantly prolonged half-life of approximately 5 days, making it
appropriate for once-weekly administration.

Dulaglutide is administrated in combination with other drugs, together with exercise and diet, to improve glycemic control. Dulaglutide is administrated once a week as a 0.75-mg dose by subcutaneous injection at any time, regardless of meal timing,

and the dose can be increased to 1.5 mg per week for additional glycemic control.

Therapeutic concentrations are achieved within 1–3 days and are steadily maintained during 2–4 weeks after weekly drug administration. However, dulaglutide is not recommended for patients with type 1 diabetes or patients whose diabetes is uncontrollable with diet and exercise.

### 8. Dulaglutide in clinical trials

AWARD (The Assessment of Weekly AdministRation) clinical trials were conducted to determine the efficacy of dulaglutide for achieving glycemic control in T2D and included a variety of phase 3 trials. Dulaglutide was compared to twice-daily exenatide, insulin glargine, metformin, and liraglutide in combination with background therapy, depending on the trial. In the AWARD-1 trial (Efficacy and Safety of Dulaglutide Added On to Pioglitazone and Metformin Versus Exenatide in T2D in a Randomized Controlled Trial), randomized participants were received once-weekly dulaglutide 1.5-mg or exenatide twice daily (10-μg) with background therapy of metformin and pioglitazone. Participants receiving a 1.5-mg dose of dulaglutide experienced dose-dependent reduction in HbA1c level by about 1.51%, while patients receiving twice-daily exenatide showed 0.99% reduction. The 2 groups had similar weight loss, 1.3 kg, and both groups experienced similar incidences of gastrointestinal side effects. Overall, under the background therapy of metformin and pioglitazone, once-weekly dulaglutide therapy has superior clinical efficacy without any tolerability and side effect than twice-daily exenatide therapy. In the AWARD-2 trial (Efficacy and Safety of Once Weekly Dulaglutide vs. Insulin Glargine in Combination with Metformin and Glimepiride in T2D Patients), 0.75- and 1.5-mg doses of once-weekly dulaglutide were compared with a 1.5-mg dose of insulin glargine, titrated to target a fasting blood glucose level around 100 mg/dL, based on metformin treatment. In this study, dulaglutide-treated participants exhibited a 0.9% reduction in HbA1c with the 0.75 mg dulaglutide dose, 0.59% reduction with the 1.5-mg dulaglutide dose, and 0.62% reduction with insulin glargine. Also, dulaglutide-treated participants experienced dose-dependent weight loss, while the insulin glargine-treated group showed almost 1.28-kg weight gain. These results demonstrate that a 1.5-mg dose of dulaglutide is superior to insulin glargine, and that a 0.75-mg dose of dulaglutide is noninferior to insulin glargine.

In the AWARD-6 trial (once-weekly dulaglutide versus once-daily liraglutide in metformin-treated patients with T2D), participants received a 1.5-mg dose of dulaglutide once weekly or a 1.8-mg dose of liraglutide once daily, with background metformin therapy, for 26 weeks. At the termination of the study, the dulaglutide group and the liraglutide group showed a decrease in HbA1c levels of 1.42% and 1.36%, respectively (P<0.0001). The liraglutide group demonstrated significantly higher weight loss compared to the dulaglutide group (3.6 kg vs. 2.9 kg, P<0.001). Also, no significant differences were observed between the 2 groups with respect to adverse effects. This study showed that once-weekly dulaglutide has noninferiority to once-daily liraglutide in reducing HbA1c with a similar safety profile.

### Conclusions

GLP-1R agonist therapies are breakthrough medications for patients with T2D and can help them achieve weight loss, improve β-cell function, and reduce a risk of causing hypoglycemia. In addition, GLP-1R agonist therapy has a variety of dosing cycles, such as once-daily injections, twice-daily injections, and once-weekly injections, which was summarized in Table 1. GLP-1R agonists have the advantage of being able to choose the appropriate agent according to the patient’s various lifestyles. In conclusion, optimally employing GLP-1R agonists, better glycemic control can be enabled.

### Conflict of interest

No potential conflict of interest relevant to this article was reported.

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