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Glucagon-like peptide-1 receptor agonists in type 2 diabetes mellitus: a brief review

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ABSTRACT

Clinical management of hyperglycemia in patients with type 2 diabetes mellitus is guided not only by published treatment algorithms, but also by consideration of recent evidence and through expert consultation. Recent studies have increased the amount of information regarding the use of glucagon-like peptide-1 receptor agonists. These are a relatively new class of drugs used for management of type 2 diabetes mellitus. They offer a unique and innovative treatment for the management of type 2 diabetes mellitus and demonstrate benefits not only in regard to blood glucose control, but potentially improving other diabetes-related comorbid conditions such as hypertension, hyperlipidemia, and obesity. As the number of glucagon-like peptide-1 receptor agonists continues to become available, physicians will soon face the challenge of selecting the right option for their patients' needs. These compounds, although all based on the effects of native glucagon-like peptide-1, differ with regard to structure, pharmacokinetics, and size, which

RESUMEN

El manejo clínico de la hiperglucemia en pacientes con diabetes *mellitus* tipo 2 (DM2) es guiado no sólo por los algoritmos de tratamiento publicados, sino también por la consideración de la evidencia reciente y mediante consultas con expertos. Estudios recientes han incrementado la cantidad de información sobre el uso de los agonistas del receptor del péptido similar al glucagón tipo 1 (arGLP-1). Los arGLP-1 son relativamente una nueva clase de fármacos que se utilizan para el manejo de la DM2. Ofrecen un avance único e innovador para el tratamiento de la DM2, y muestran beneficios no sólo sobre el control de la glucosa, sino que potencialmente mejoran otras condiciones comórbidas relacionadas con la diabetes, como la hipertensión, la hiperlipidemia y la obesidad. Debido a la disponibilidad de distintos arGLP-1, los médicos se enfrentan al reto de seleccionar la opción adecuada a las necesidades de sus pacientes. Estos compuestos, aunque todos ellos están basados en los efectos del péptido similar al glucagón tipo 1 nativo, difieren con

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ultimately leads to different clinical effects. (REV MEX ENDOCRINOL METAB NUTR. 2016;3:137-48)

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respecto a la estructura, la farmacocinética y el tamaño, lo que conduce finalmente a diferentes efectos clínicos.

Palabras clave: Agonistas del receptor de GLP-1. Diabetes *mellitus* tipo 2. Exenatida. Lixisenatida. Liraglutida. Dulaglutida. Exenatida semanal.

INTRODUCTION

Type 2 diabetes mellitus (T2DM) is a chronic progressive disease resulting from dysregulation of glucose homeostasis, characterized by insulin resistance and progressive insulin secretory impairment. At least 90% of all patients with diabetes are classified as having T2DM[1]. The prevalence of T2DM is increasing at an astounding rate, affecting an estimated 415 million adults worldwide[2]. The progressive nature of T2DM indicates that, although management initially relies on lifestyle modifications, it invariably requires pharmacological intervention to achieve and maintain blood glucose levels as close as possible to the normal range[3]. Recent advances in the pathophysiology of diabetes have been accompanied by improvements in the pharmacological options available to tackle the condition[4]. One such relatively recent addition is a class of drugs whose mechanism of action is based upon the incretin pathway. These incretin hormones play a crucial role in glucose metabolism, including glucose-dependent potentiation of insulin synthesis by pancreatic ß-cells and glucagon suppression. In addition to effects on glucose homeostasis, incretin-based therapies slow the rate of gastric emptying, which not only reduces postprandial glucose levels, but also induces early satiety and decreased food intake. Incretin-based therapeutic approaches include the injectable glucagon-like peptide-1 receptor agonists (GLP-1 RAs), also known as glucagon-like peptide 1 analogues[5]. This article reviews the various GLP-1 RAs currently available in Mexico, specifically focusing on the characteristics of these drugs and their clinical efficacy in T2DM.

INCRETIN HORMONES AND DIABETES

The incretin concept was reported more than 100 years ago[6]. Inspired by Bayliss and Starling's discovery of secretin, Moore, et al. hypothesized in 1906 that gut extracts contained a hormone that regulates the endocrine pancreas.

The incretin effect describes the phenomenon that individuals have greater insulin secretion following oral glucose challenges as opposed to intravenous glucose, suggesting that gastrointestinal hormones are responsible for a portion of insulin secretion. Abnormalities in the incretin axis have been shown to play an important role in the progressive ß-cell failure of T2DM. Patients diagnosed with T2DM had significantly lower glucagon-like peptide-1 (GLP-1) concentrations stimulated by caloric intake when compared to individuals without diabetes. Because GLP-1 deficiency occurs early in the natural history of T2DM, it follows that GLP-1 replacement therapy is a logical choice to restore the deficient insulin response characteristic of the diabetic condition[7].

GLUCAGON-LIKE PEPTIDE-1

Glucagon-like peptide-1 is released by the enteroendocrine L-cell, which is found in greater numbers in the epithelium of the distal ileum and colon of rodents and humans. In humans, GLP-1 secretion in response to nutrient ingestion is biphasic, with both an early (30-45 minutes) and a later (60-90 minutes) peak[8]. GLP-1 acts through the GLP-1

receptors, which are found in organs as varied as the brain, lung, pancreatic islets, stomach, hypothalamus, heart, intestine, and kidney. Because native GLP-1 has a very short plasma half-life (~ 2-3 minutes) and is inactivated by the dipeptidyl peptidase-4 (DPP-4) enzyme, it cannot be used therapeutically except by continuous intravenous infusion[9]. Modifying the two sites in the GLP-1 molecule that are susceptible to cleavage (the position 8 alanine and the position 34 lysine) can help prolong the half-life of GLP-1. These and other chemical modifications help in creating compounds known as GLP-1 RAs, which have a longer half-life and can be used for therapeutic purposes[10].

Mechanism of action

The GLP-1 RAs act by increasing the concentration of GLP-1 to supraphysiological or pharmacological levels. This stimulates GLP-1 receptors present in various organs of the body to elicit beneficial glycemic effects. This class of injectable antihyperglycemic agents acts in a glucose-dependent manner and reduces both fasting and postprandial blood glucose levels. GLP-1 RAs improve glucose homeostasis through multifaceted action. They enhance glucose-dependent insulin secretion and induce insulin biosynthesis, suppress inappropriately elevated glucagon levels both in fasting and postprandial states, and slow gastric emptying. Slowing of gastric motility plays an important role in reducing postprandial glycemic excursions[11].

Classification of glucagon-like peptide-1 receptor agonists

The GLP-1 RAs are classified according to their basic structure and pharmacokinetic properties. Structurally, one group exploits the native GLP-1 with some amino acid alterations, making it resistant to degradation by the DPP-4 enzyme. The other group was synthetically developed by replicating the structure of a naturally occurring protein, exendin-4, with substantial homology to native GLP-1. Like native GLP-1, this protein has GLP-1 RA-activating properties and is naturally resistant to degradation by the DPP-4 enzyme[12].

Apart from structural classification, these drugs can also be classified based on the duration of their action, i.e. short-acting and long-acting GLP-1 RAs. Whereas the short-acting receptor agonists are characterized by large-amplitude fluctuations in plasma peptide levels when administered at typical intervals, treatment with the long-acting compounds at their typical administration intervals leads to a more consistent, supraphysiological activation of the GLP-1 receptor[13,14]. Some of the strategies used to prolong the life of these compounds include albumin binding to prevent renal filtration, conjugation to a modified IgG4 Fc fragment, and coupling of the molecule to microspheres to delay absorption from the subcutaneous site. These differences in structure and pharmacokinetic profiles between short- or long-acting analogues (Table 1) have fundamental implications for the mode of action, efficacy, and tolerability of these compounds[15].

SHORT-ACTING GLUCAGON-LIKE PEPTIDE-1 RECEPTOR AGONISTS

Resistance to cleavage by DPP-4 confers a plasma half-life of ~ 2-4 hours for the short-acting GLP-1 RAs, exenatide and lixisenatide[16,17]. As a consequence, these compounds activate the GLP-1 receptor for only ~ 6 hours after each injection. The recommended dosing intervals are twice daily for exenatide and once daily for lixisenatide, indicating that only modest efficacy can be expected during the fasting state, after lunch, and during the night (during which periods plasma levels of these drugs decline to baseline levels). The effects of these drugs on fasting glucose levels or fasting measures of insulin secretion are less pronounced than those of long-acting analogues[14]. In contrast, the rapid increases in plasma levels of these short-acting receptor agonists lead to substantial retardation of gastric emptying, thereby blunting markedly postprandial glucose excursions[13,14,17].

Although the two short-acting receptor agonists stimulate insulin secretion in the fasting state and under experimental conditions, their effects on postprandial blood glucose levels do not seem to be mediated by

Table 1. Chemical properties and pharmacokinetic profiles of glucagon-like peptide-1 receptor agonists

GLP-1 RA	Structure	Half-life	Dosing frequency	Dose	Baseline A1C	Reduction of A1C
			Short-acting			
Exenatide	Synthetic version of naturally occurring exendin-4 peptide from the Gila monster *Heloderma suspectum*; 53% homology with native human GLP-1	2.4 hours	Twice daily	5-10 µg	7.8-8.5%	0.8-1.5%
Lixisenatide	Synthetic analog of endogenous exendin-4 with the addition of six lysine residues at the C-terminal; 50% homology with native human GLP-1	3-4 hours	Once daily	10-20 µg	7.6-8.4%	0.7-1.0%
			Long-acting			
Liraglutide	Acylated GLP-1 analogue that shares 97% amino acid sequence homology to human endogenous GLP-1	11-13 hours	Once daily	1.2-1.8 mg	8.1-8.5%	0.8-1.5%
Dulaglutide	Recombinant fusion protein consisting of two identical disulfide-linked chains, each with an N-terminal GLP-1 analog sequence covalently linked to the Fc section of modified human immunoglobulin G4 heavy chain (IgG4 Fc); GLP-1 analog portion is 90% homologous to native human GLP-1	5 days	Once weekly	0.75-1.5 mg	7.6-8.5%	0.8-1.6%
Exenatide once-weekly	Once-weekly formulation produced by encapsulation of parent exenatide molecule in PLG microspheres	NA	Once weekly	2 mg	8.3-8.6%	1.3-1.9%

A1C: hemoglobin A1c; GLP-1 RA: glucagon-like peptide-1 receptor agonist.

stimulation of insulin secretion[18,19]. In fact, postprandial insulin secretion is dose-dependently reduced by exenatide and lixisenatide. Indeed, the postprandial reduction of blood glucose levels induced by short-acting GLP-1 RAs seems to be primarily the result of delayed gastric emptying, which leads to a decreased rate of glucose entry into the duodenum and, subsequently, into the circulation[20]. This mechanism explains why short-acting GLP-1 RAs seem to exert an insulin-lowering effect in the postprandial state, despite the well-characterized insulinotropic effect of GLP-1 itself[13].

EXENATIDE

Exenatide (Baietta®) was the first of the new incretin mimetic class of antihyperglycemic agents to be marketed (in 2005 in the U.S. and in 2006 in Europe). It has been available in Mexico since 2008[21-22]. Exenatide is a synthetic version of the natural 39-amino acid peptide exendin-4 found in salivary secretions of the Gila monster (*Heloderma suspectum*) and shares 53% amino acid sequence homology with human GLP-1[23]. Exenatide is an incretin mimetic. Because it is a GLP-1 RA, it binds to and stimulates the human pancreatic GLP-1 receptor with an affinity equal to that of GLP-1. However, GLP-1 is degraded by the enzyme DPP-4 and has a very short half-life of 2-3 minutes in the circulation, whereas exenatide is resistant to degradation by DPP-4 and, as a result, has an extended plasma half-life of ~ 2.4 hours and very high *in vivo* activity compared with GLP-1. It remains detectable in plasma for ~ 10 hours after a single dose[24].

Exenatide is available in a prefilled pen device and is administered subcutaneously twice daily (BID)

within 60 minutes before two major meals. The initial dose is 5 µg BID that, if well tolerated by the patient, may be titrated to 10 µg BID after one month[21].

Because exenatide restores the first-phase insulin response, injections should be administered prior to meal times and not after eating. Specifically, exenatide is indicated as a twice-daily injection, administered within the 60-minute window prior to eating the two main meals of the day. To minimize the potential risk of hypoglycemia, each injection should be given at least six hours apart[25].

Efficacy

Three pivotal 30-week, phase III clinical trials, referred to as the AC2993 Diabetes Management for Improving Glucose Outcomes (AMIGO) program, investigated the efficacy and safety of exenatide BID in patients treated with metformin alone, patients treated with a sulfonylurea alone, and patients treated with both metformin and a sulfonylurea[25-27]. Reduction in glycosylated hemoglobin A1c (A1C) in these trials with 10 µg of exenatide BID ranged from ~ 0.8-0.9% and decrease in weight observed from baseline was up to ~ 2.8 kg. The durability of glycemic effect was noted for up to three years[26-28].

The slowing of gastric emptying has the likely effect of reducing postprandial glucose excursions in some of these trials[27]. However, because the half-life of exenatide is short, it may not be sufficient to control postprandial glucose surges in all patients, and fasting plasma glucose reductions are lower than those of longer-acting drugs[29].

Safety

The most common adverse effect is mild-to-moderate nausea and vomiting, which decreased with time. The incidence of hypoglycemia is low, except when exenatide is used in combination with a sulfonylurea or insulin. Exenatide is not recommended for use in patients with end-stage renal disease or severe renal impairment. In patients with moderate renal impairment, dose escalation from 5 to 10 µg should proceed conservatively. Formation of anti-exenatide antibodies has been reported with relatively high frequency, which may be a result of only 53% homology to the native GLP-1 molecule and its nonhuman origin. The presence of these antibodies generally did not impact the glycemic response in these patients[21].

LIXISENATIDE

Lixisenatide (Lyxumia®) was synthesized by Zealand Pharma and subsequently licensed by Sanofi for development and commercialization. It was approved in Mexico in 2013[30]. Lixisenatide is a synthetic analog of endogenous exendin-4 that acts as a selective GLP-1 RA. Compared with exendin-4, lixisenatide contains a C-terminal modification of the addition of six lysine residues and deletion of a proline that increases its binding affinity to the GLP-1 receptor and increases its circulating half-life[31]. Lixisenatide has a four-fold higher binding affinity of the GLP-1 receptor compared with native GLP-1. Like other GLP-1 RAs, lixisenatide suppresses inappropriate glucagon secretion from pancreatic α-cells, stimulates glucose-dependent insulin secretion by pancreatic β-cells, and increases satiety by delaying gastric emptying[32].

The initial dose of lixisenatide is 10 µg subcutaneously once daily for 14 days followed by 20 µg once daily thereafter. It is recommended that lixisenatide be administered within one hour of the same meal each day. Lixisenatide has a half-life of 3-4 hours[33].

Efficacy

The ability of lixisenatide to reduce A1C, fasting plasma glucose, and body weight is similar to or less than other GLP-1 RAs and DPP-4 inhibitors; however, lixisenatide has a pronounced ability to decrease postprandial glucose. This feature distinguishes it from the longer-acting GLP-1 RAs and makes it an ideal agent for patients who experience postprandial excursions[30].

Lixisenatide (20 µg) has been clinically evaluated in the GetGoal Program, which included monotherapy, add-on therapy to metformin, sulfonylurea or pioglitazone, and in combination with basal insulin. In addition to GetGoalX, which had an active comparator (exenatide), all these trials compared lixisenatide to placebo[34-41]. Lixisenatide showed a significant decrease in A1C from baseline in these trials, ranging from 0.7-1.0%, with an accompanying weight loss of 0.2-2.8 kg. Lixisenatide has a moderate effect on fasting plasma glucose and a predominant effect on postprandial plasma glucose, attributed to a reduction in gastric emptying[33].

The ELIXA study evaluated the effects of lixisenatide on cardiovascular (CV) outcomes in patients with T2DM who experienced a recent acute coronary event. In addition to the positive effects of lixisenatide on glycemic control and weight loss, no differences were observed for the primary endpoint (major CV adverse effects) including hospitalization for heart failure and deaths from CV-related causes between lixisenatide and placebo groups[42].

Safety

The main adverse effects are gastrointestinal in nature. Lixisenatide is potentially immunogenic and 69.8% of patients had a positive antibody status. The presence of these antibodies did not impact the glycemic response in these patients. Lixisenatide is mainly eliminated through the kidneys and should be used with caution in patients with moderate renal impairment. Use is not recommended in patients with severe renal impairment or end-stage renal disease[33].

LONG-ACTING GLUCAGON-LIKE PEPTIDE-1 RECEPTOR AGONISTS

Plasma levels of the long-acting GLP-1 RAs (exenatide once-weekly, dulaglutide, and liraglutide) are all continuously elevated throughout the periods between doses at their respective recommended injection intervals. These drugs provide better glycemic control than the short-acting GLP-1 RAs because patients have higher insulin levels in the fasting state (and presumably during the night) following administration of long-acting receptor agonists[43]. The long-acting compounds probably have a greater effect on blood glucose levels than short-acting receptor agonists because they are also effective during the night and early morning when the interval between doses of short-acting receptor agonists is long and the plasma concentration of these drugs falls[15].

The mode of action of long-acting GLP-1 RAs differs from that of the short-acting compounds. For instance, unlike the short-acting compounds, the long-acting GLP-1 RAs do not seem to have a substantial effect on gastric motility when administered in the long term. This lack of an effect on the rate of gastric emptying of the long-acting GLP-1 RAs is probably due to tachyphylaxis, meaning that the effect of these compounds on gastric emptying decreases rapidly with time as a result of their continuous activation of the GLP-1 receptor[43].

Long-acting GLP-1 RAs do not lower postprandial glucose excursions to the same extent as short-acting compounds[29]. The appetite-suppressing action of GLP-1 has long been thought to be secondary to its role in delaying gastric emptying. However, reductions in body weight observed in individuals receiving a short-acting GLP-1 RA are comparable to those seen in patients treated with long-acting compounds[44].

LIRAGLUTIDE

Liraglutide (Victoza®) is an analog of human GLP-1 produced by recombinant DNA technology. It was approved for clinical use in Europe in 2009 and in the USA in 2010 and has been available in Mexico since 2009[45].

Liraglutide is an acylated GLP-1 analogue that shares 97% amino acid sequence homology to human endogenous GLP-1. The single amino acid substitution of lysine with arginine at position 34 and the attachment of a C16 fatty acid chain to lysine at position 26 enables liraglutide to self-associate and form a

heptametrical structure, which delays absorption from the subcutaneous injection site and provides protection against degradation by DPP-4 enzyme and neutral endopeptidases. As a consequence, liraglutide has a much longer half-life (11-13 hours) than endogenous GLP-1 (≈ 13 hours vs. 1.5-2.0 minutes), making it suitable for once-daily administration[46-49].

Liraglutide should be initiated at a dose of 0.6 mg once daily for one week and then titrated to 1.2 mg daily. If the 1.2 mg dose does not achieve glycemic goals, the dose can be further increased to 1.8 mg daily. Liraglutide is available in disposable, prefilled, and multi-dose pens[48].

Efficacy

Liraglutide has been investigated in a clinical development program called Liraglutide Effect and Action in Diabetes (LEAD)[50-54], which compared the two doses (1.2 and 1.8 mg) of liraglutide with glimepiride, rosiglitazone, and insulin glargine as well as a direct comparison (LEAD 6) between liraglutide (1.8 mg) and exenatide. The duration of the studies varied from 26-52 weeks. The A1C reduction from baseline in the LEAD trials varied between 0.8 and 1.5% for the 1.2-mg arm and 1.0-1.5% for the 1.8 mg arm. Change in weight observed with liraglutide in the LEAD trials varied from +0.3 to −1.2 kg for the 1.2 mg arm and −0.2 to −2.6 kg for the 1.8 mg arm. Liraglutide alone or in combination with oral antihyperglycemic agents was shown to be superior to placebo and active comparators in all LEAD trials except LEAD 2 where both doses were non-inferior to glimepiride for lowering A1C. Liraglutide had a modest effect on the reduction of gastric emptying, and thus the reduction in postprandial glucose excursions can be mainly attributed to a reduction in preprandial glucose levels. In a head-to-head trial with long-acting release exenatide, there was a greater reduction in fasting plasma glucose with liraglutide, whereas better postprandial glucose reduction was seen with long-acting release exenatide after breakfast and dinner[55].

It was recently reported that liraglutide significantly reduced the risk of heart attack or stroke in the LEADER (Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results) trial. The trial compared the addition of either liraglutide or placebo to standard of care and met the primary end point of showing non-inferiority as well as demonstrating superiority, with a statistically significant reduction in CV risk (–13%). Thus, the use of liraglutide in combination with other glucose-lowering drugs will be an additional effective treatment option for patients with T2DM presenting with a high CV risk[56].

Safety

The most common adverse events were gastrointestinal in nature and tended to decrease over time. The rate of hypoglycemia was low except when liraglutide was used in combination with sulfonylureas when there was an increased risk of hypoglycemia. Anti-liraglutide antibodies were detected in 8.6% of liraglutide-treated patients. In general, the presence of antibodies did not impact the clinical efficacy. No dose adjustment is recommended for patients with mild renal impairment. Liraglutide is not recommended in patients with end-stage renal disease[48].

DULAGLUTIDE

Dulaglutide (Trulicity®) received U.S. FDA approval in September 2014 and approval in Europe in November 2014. It has been available in Mexico since 2015[57].

Dulaglutide is a long-acting GLP-1 analog covalently linked to human IgG Fc fragment, modified to increase the duration of pharmacodynamic activity. Dulaglutide reduces DPP-4 inactivation, increases solubility, and reduces immunogenicity. The increased duration of its pharmacodynamic activity can be attributed to its diminished renal clearance, resulting in a plasma half-life of ~ 5 days, allowing for once-weekly dosing[58,59].

Administered as a 0.75-mg injection, the dose can be escalated to 1.5 mg once weekly to achieve glycemic targets. Therapeutic concentrations are achieved

faster with dulaglutide compared to other once-weekly GLP-1 RAs within 1-3 days, whereas steady state concentrations occur within 2-4 weeks after administration of the once-weekly injection. The extended duration of the action of dulaglutide is due to modified amino acid sequences that resist DPP-4 degradation as well as to the large size of the molecule, reducing its renal clearance. Dulaglutide is available in Mexico in a ready-to-use prefilled pen syringe[58].

Efficacy

The regulatory approvals of dulaglutide were based on the Assessment of Weekly Administration of LY2189265 in Diabetes (AWARD) 1-5 trials. In these trials, two doses of dulaglutide once weekly, 0.75 and 1.5 mg, were compared to placebo, long-acting release exenatide, insulin glargine, metformin, and sitagliptin; dulaglutide 1.5 mg was compared to liraglutide 1.8 mg. The duration of these trials ranged from 26 to 104 weeks. The 1.5 mg dose further demonstrated superiority to its active comparators in all five registration trials and no inferiority to liraglutide 1.8 mg in the AWARD-6 trial. In various AWARD studies, A1C reduction with the 1.5 mg dose ranged from 0.8-1.6%. Similarly, weight loss of up to 3.2 kg was seen. In comparison to placebo, dulaglutide showed clinically significant reductions in fasting plasma glucose levels. Dulaglutide is the only GLP-1 RA so far to achieve non-inferiority to liraglutide 1.8 mg as demonstrated in a head-to-head study (1.42% dulaglutide vs. 1.36% liraglutide, $p < 0.001$)[60-66].

Safety

The most common adverse events were gastrointestinal in nature. Dulaglutide exhibited a relatively low immunogenicity, with 1.6% of treated patients in the clinical trials developing anti-drug antibodies[58].

EXENATIDE ONCE WEEKLY

Exenatide once weekly (Bydureon®) was approved in Europe in 2011 and in the USA in 2012. It has been available in Mexico since 2013 and was the first once-weekly GLP-1 RA to receive FDA-approved labeling as adjunctive therapy to diet and exercise for patients with T2DM[67]. The long-acting formulation contains the active ingredient of the original exenatide BID formulation dispersed in microspheres of medical-grade poly-(d,l-lactide-co-glycolide) in an aqueous formulation[68]. Exenatide once weekly has a unique pharmacokinetic profile. Upon administration, 1-2% of the drug is immediately available; the remaining amount, as microspheres, is gradually released over a 10-week period. At approximately week 2, an initial peak with the release of surface-bound exenatide occurs, correlating with the onset of a potential glucose-lowering effect. At week 6 or 7, a steady-state period occurs as the drug is gradually released from the microspheres. If the patient discontinues exenatide once weekly, plasma levels will fall to an undetectable concentration in 10 weeks[69]. Exenatide once weekly is administered as a 2 mg subcutaneous injection and is available in two formulations, one as a single-dose vial that requires patient reconstitution with diluent, and another as a ready-to-use prefilled injection pen[67]. The two formulations are currently available in Mexico.

Efficacy

The clinical efficacy of exenatide once weekly has been determined through several randomized controlled studies including the Diabetes Therapy Utilization: Researching Changes in A1C, Weight and Other Factors through Intervention with Exenatide Once Weekly (DURATION trials)[70-75]. The DURATION-2 trial found that exenatide once weekly may be more effective than sitagliptin or pioglitazone for improving glycemic control, reducing A1C levels from baseline by 1.5% compared with 0.9% with sitagliptin ($p < 0.0001$) and 1.2% with pioglitazone ($p = 0.0165$). Exenatide once weekly also reduced weight in patients with T2DM from baseline by 2.3 kg compared with 0.8 kg with sitagliptin ($p = 0.0002$) and a gain of 2.8 kg with pioglitazone ($p < 0.0001$)[71]. The DURATION-3 trial concluded that exenatide once weekly may be more effective than insulin

glargine for improving glycemic control, reducing A1C levels from baseline by 1.5% compared with 1.3% with insulin glargine ($p = 0.017$) as well as reducing weight from baseline by 2.6 kg compared with a gain of 1.4 kg with insulin glargine ($p < 0.0001$). However, in this study, patients and investigators were asked to adhere to titration targets, but forced titration was not used[72]. The DURATION-6 trial showed that liraglutide may improve glycemic control compared with exenatide long-acting release; liraglutide reduced A1C from baseline by 1.48% compared with 1.28% in the exenatide group ($p = 0.02$)[75]. Exenatide once weekly would not be an appropriate pharmacotherapeutic option vs. insulin therapy in patients who are glucotoxic or have an A1C of 9% or greater.

Safety

Gastrointestinal complaints were the most commonly reported adverse events. There was a wide variation in the rates of nausea (12.0-26.4%). The nausea was intermittent and peaked as the drug levels approached steady state after 6-8 weeks of therapy. Vomiting occurred in 4.0-10.8% of patients and seemed to correlate with the increased rate of nausea[76].

Exenatide once weekly is not recommended for use in patients with end-stage renal disease and should be used with caution in moderate renal impairment. Small, asymptomatic, subcutaneous injection-site nodules can be seen, consistent with the known properties of microspheres[76]. Approximately 49% of patients during the five active comparator-controlled trials had anti-exenatide antibodies during the trial; however, this did not appear to affect glycemic response[67].

GLUCAGON-LIKE PEPTIDE-1 RECEPTOR AGONISTS IN CLINICAL PRACTICE

According to guidelines from the American Diabetes Association (ADA) and European Association for the Study of Diabetes (EASD), the standard-of-care treatment for patients diagnosed with T2DM is metformin in addition to lifestyle changes[1,77].

The American Association of Clinical Endocrinologists' treatment algorithm published in 2016 recommends metformin, GLP-1 RAs, sodium-glucose co-transporter 2 (SGLT2) inhibitors, DPP-4 inhibitors, or alpha-glucosidase inhibitors as initial choices for monotherapy for patients with A1C $< 7.5\%$ at diagnosis. For patients with initial A1C $\geq 7.5\%$, dual combination therapy with metformin is recommended. GLP-1 RAs are recommended as the first-line add-on therapy to metformin in this patient population followed by SGLT2 inhibitors, DPP-4 inhibitors, thiazolidinediones, basal insulin, alpha-glucosidase inhibitors, or sulfonylureas. For patients with initial A1C > 9.0% without symptoms of hyperglycemia, dual or triple combination therapy with metformin or another first-line agent (without insulin) is recommended, whereas for patients with A1C > 9.0% and hyperglycemia symptoms, insulin therapy with or without metformin or other oral glucose-lowering agents is recommended[78,79].

The recently updated ADA/EASD treatment guidelines propose that in patients who are not within control targets with basal insulin plus metformin, the combination of a GLP-1 RA with basal insulin may be a better option than intensified basal-plus or basal-bolus due to the advantages of the combination[77]. GLP-1 RAs are appealing because of their high glucose-lowering effect, potential for weight loss, and low risk of hypoglycemia. Because of the relative cost compared with metformin and the subcutaneous route of administration, GLP-1 RAs are generally not considered a first-line monotherapy[80].

BEYOND GLYCEMIC CONTROL

The wide distribution of GLP-1 receptors leads to the suggestion that, despite the principal effect of regulating glycemia, their other effects are varied and multifocal. Some of the pleiotropic effects of

GLP-1 RAs in experimental and clinical findings include the following[81-86]:

– Cardiovascular system: positive effect on myocardial contractility, hypertension (natriuretic/diuretic effect), endothelium (anti-atherosclerotic), and lipid profile.

– Nervous system:

• Neuronal protection, resulting in an improvement in cognition, memory, and spatial learning.

• Modification of eating behavior by inducing satiety, thereby reducing energy intake by ~ 12%.

• Gastric slowing via interaction with the peripheral nervous system (vagus), thus inducing postprandial satiety.

– Obesity: weight loss is dose-dependent and progressive. Liraglutide has shown to induce a mean weight loss of ~ 6 kg with > 35% of the subjects achieving ≥ 10% reduction of weight.

– Insulin resistance: restoration of insulin signaling and reduction of hepatic gluconeogenesis. Reduced insulin resistance, locally at the level of ß-cell and fat cell (reduced release of free fatty acids) and systemically (down-gradation of markers of inflammation).

– Gastrointestinal/hepatobiliary system:

• Delay of gastric emptying via "ileal-break mechanism".

• Improve hepatosteatosis.

– Renal system: reduction of albuminuria, independent of the presence of other poor prognostic markers.

– Bone health: improves bone mass via its antagonistic action on neuropeptide Y.

– Skin: potential beneficial role of liraglutide and exenatide in psoriasis via influence on natural killer cells (implicated in pathogenesis of psoriasis).

These effects must be demonstrated in clinical practice so that subsequent revisions will be required in this regard. It must be noted that all these uses, except for obesity, are not approved and are presently off-label.

FUTURE TRENDS

Currently available GLP-1 RAs are highly beneficial in the treatment of patients with T2DM. Future developments in this class of drugs may result in further improvements in glycemic control and in the convenience of dosing regimens, thereby broadening their acceptability and therapeutic spectrum (i.e. albiglutide, semaglutide, efpeglenatide)[87]. Another use of this class of drugs will be their combination with insulin, i.e. LixiLan (lixisenatide and insulin glargine) and IDegLira (liraglutide and insulin degludec)[88,89].

As the mechanism of action of GLP-1 RAs is elucidated, further potential uses for these drugs may also be found[86]. Their use is likely to increase in the near future. They will be used not only in diabetes, where they help achieve composite endpoints of glycemic control, weight loss and lack of hypoglycemia, but also in prediabetes and in obesity.

CONCLUSIONS

Our understanding of diabetes is constantly evolving and GLP-1 RAs represent an important facet of this understanding. This class is being recognized as an important therapy in the management of T2DM, offering many advantages over other agents including weight loss, potential ß-cell protection, and low risks of hypoglycemia. The differences between the GLP-1 RAs enable physicians to choose the compound with the clinical profile most likely to benefit the patients. Although long-term safety data are unavailable due to the short duration that these agents have been on the market, future studies will provide guidance to practitioners on the appropriate choice of agents to mitigate risk. Overall, GLP-1 RAs are effective and innovative agents for patients with T2DM who are either uncontrolled or intolerant to first-line metformin therapy.

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DISCLOSURE OF INTEREST

No conflict of interest is reported with regard to this manuscript. The authors declare no competing interests with the mentioned pharmaceutical companies.

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