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EXENATIDE EXTENDED RELEASE

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Abstract

Exenatide once weekly (ExeOW,Bydureon Astra Zeneca), a drug belonging to the class of glucagon-like peptide-1 (GLP-1)receptor agonists, is the first agent approved for treatment of type 2 diabetes that can be administered on a weekly basis. Exenatide once-weekly is under development as monotherapy as an adjunct to diet and exercise or as a combination therapy with an oral antidiabetes drug in adults with type 2 diabetes. This long-acting formulation contains the active ingredient of the original exenatide twice-daily formulation encapsulated in 0.06-mm-diameter microspheres After mechanical suspension and subcutaneous injection by the patient.A small amount of loosely bound surface exenatide, typically less than 1%,releases in the first few hours, whereas drug located in deeper interstices diffuses out more slowly (time to maximum,2 d and glycolic acid,which are subsequently eliminated as carbon dioxide and water. For EQW, plasma exeweeks).Fully encapsulated exenatide (i.e, drug initially inaccessible to diffusion) releases over a still longer period (time to maximum 7 weeks) as the PLG matrix hydrolyzes into lactic acinatide concentrations reach the therapeutic range by 2 weeks and steady state by 6–7 weeks.In comparative trials, EQW improved hemoglobin A1c more than EBID, sitagliptin, pioglitazone, or insulin glargine and reduced fasting plasma glucose more than EBID. EQW is the first glucose-lowering agent that is administered once weekly.

Introduction

Exenatide, sold under the brand name Byetta, is a prescription injection used to treat type 2 diabetes.Glucagon-like peptide-1 (GLP-1) is a 30-amino acid peptide hormone produced by the intestinal epithelial endocrine L cells through differential processing of proglucagon. It is secreted in response to a meal and plays an important role in glycemic control by acting on multiple organs and metabolic pathways. GLP-1 is responsible for 50–70% of the total postprandial insulin secretion in a glucose-dependent manner [1]. Its action on the pancreatic endocrine system also includes stimulation of insulin biosynthesis, reduction of glucagon secretion, modulation of insulin sensitivity of beta cells and, at least in animal models, a positive action on beta cell mass itself. Once secreted, GLP-1 is degraded within minutes. Antihyperglycemic agents available with which to address this complex chronic metabolic disease. These agents are increasingly being used as part of combination therapy strategies as we acknowledge the multifactorial pathophysiology of T2DM Incretin-based therapies, which include both the glucagon-like peptide-1 receptor agonists (GLP-1 RAs) and the dipeptidyl peptidase4 (DPP-4) inhibitors meet these criteria[2,3]. GLP-1 RAs are known to be more efficacious than DPP-4 inhibitors by virtue of their supraphysiologic delivery of GLP-1 versus inhibition of degradation of native GLP-1 and have greater effects on weight loss, but have less favorable tolerability profiles.[4] Of these, exenatide twice daily was the first GLP-1 RA to be commercially developed [5]. Today, an extended-release formulation of exenatide exists that can be administered once weekly 12 most recently, this agent has become available in a pen delivery device. loss, but have less favorable tolerability profiles of these, exenatide twice daily was the first GLP-1 RA to be commercially developed [6].

Definition of type-2 diabetes

Type 2 diabetes is a disease in which your blood glucose, or blood sugar, levels are too high. Glucose is your main source of energy. It comes from the foods you eat. A

hormone called insulin helps the glucose get into your cells to give them energy.

Mechanism of Action

Incretins, such as glucagon-like peptide-1 enhance glucose-dependent insulin secretion and exhibit other antihyperglycemic actions following their release into the circulation from the gut. BYDUREON is a GLP-1 receptor agonist that enhances glucose dependent insulin secretion by the pancreatic beta-cell [7]. Suppresses inappropriately elevated glucagon secretion, and slows gastric emptying. The drug class has been found to have additional therapeutic benefits such as weight loss and reduced major cardiovascular disease events in several large randomized controlled trials. The metabolic properties of these agents might also be of value for patients with type 1 diabetes (T1D), particularly those with residual insulin production. Many patients, even those with long-standing T1D, may have detectable levels of peptide well beyond the new-onset period. Tropic effects of exendin-4 on β cells were shown in rodents after partial pancreatectomy, and synergy with immune therapy at the time of diabetes onset enhanced the insulin content of β cells. Data from human studies have identified impaired function of residual β cells in patients with T1D, thus further supporting a potential use of GLP-1RAs in these patients. The results from previous clinical trials of GLP-1RAs in patients with T1D, however, were inconclusive.In addition, newer agents with weekly dosing may have a greater impact on fasting blood sugars and decreased burden of use. We therefore conducted a randomized placebo controlled trial to determine whether the long-acting GLP-1RA, exenatide extended release (ER), affected metabolic control in patients with stable management of T1D and whether there were differences in the responses in patients with and without detectable levels of endogenous insulin production, that is, with detectable C-peptide levels. In the past two decades, new anti-diabetic medications for diabetes have been developed and marketed, including incretin-based therapy, which consists of two different classes: dipeptidyl peptidase-4 (DPP-4) inhibitors and glucagon-like peptide-1 (GLP-1) receptor agonists (GLP-1 RAs). DPP-4 inhibitors enhance the plasma levels of native GLP-1 and glucose-dependent insulinotropic polypeptide by preventing their proteolytic degradations, while GLP-1 RAs display structural similarities to native GLP-1 and activate the GLP-1 receptor at a supra-physiological level.

Pharmacokinetic properties of exenatide

Exenatide in its original subcutaneous formulation reaches its mean peak concentration within 2 h and has a terminal half-life of 2.4 h. requiring twice-daily administration [8]. Exe OW has been developed by adopting an encapsulation technique that slows the release of exenatide, allowing a once-weekly subcutaneous administration. The product is to be reconstituted just before injection. The pharmacokinetics of ExeOW has been assessed in one single-dose and two multiple-dose studies in patients with T2D [9]. It is characterized by a multiphasic concentration–time profile due to the slow release of the drug in the bloodstream through the progressive dissolution of the polymeric matrix of the microspheres encapsulating exenatide The process occurs in three stages: initial phase, diffusion, and final erosion release [10]. During the diffusion phase, the drug is released at a constant rate into the bloodstream, and finally during the erosion phase the matrix is completely dissolved.

Pharmacodynamics

Exenatide ER is the long-acting formulation that contains the active ingredient of the original exenatide BID formulation. 0.06 mm diameter microspheres of medical grade poly Following injection of a single dose, exenatide is released from the microspheres over approximately 10 weeks [11]. There is an initial period of release of surface-bound exenatide, followed by a gradual release of exenatide from the microspheres that results in two peaks of exenatide in plasma at around week and weeks 6–7, respectively, representing the hydration and erosion of the microspheres. After 6 or 7 weeks, the mean plasma exenatide concentration of approximately 300 pg/mL is maintained over weekly dosing intervals, indicating that steady-state plasma concentrations have been achieved.

Evaluation of exenatide in relation to other Drugs.

Effects on Glycemic Control

ExeOW Compared to ExeBID

Two studies compared ExeOW to ExeBID testing the single-dose tray. The DURATION-1 study was designed to test non-inferiority of ExeOW as compared to ExeBID in patients receiving metformin, sulfonylurea, or thiazolidinedione monotherapy or in combination, based on the difference in the reduction of HbA1c (95% CI upper limit of the difference 0.4%).[12]Treatment within the initial randomized portion of the study had a duration of 30 weeks but subsequent cohorts of patients entered long-term uncontrolled extensions of the study up to 7 years: data up to 6 years have been published to date [13]. The slight progressive trend upward in HbA1c and FPG levels and the reduced proportion of patients attaining HbA1c below target levels noted after the first year of ExeOW treatment [14]. were probably due to the natural progression of the disease.

ExeOW Compared to Pioglitazone and Sitagliptin

ExeOW has been demonstrated to be more effective than pioglitazone and the oral DPP-4 sitagliptin as add-on treatment to metformin in a 26-week RCT testing the superiority of ExeOW in terms of HbA1c change from base line [15].

ExeOW Compared to Insulin

Treatment with ExeOW has been compared to GLAR in a randomized, superiority study conducted in patients with suboptimal glycemic control with oral antidiabetic drugs [16]. Three-year follow-up data from this study confirm the sustained long-term activity of ExeOW. Throughout the 3-year treatment period, mean HbA1c was lower in patients given ExeOW than in those given GLAR; at 3 years the mean decrease from baseline in HbA1c was still significantly greater in patients treated with ExeOW and more patients treated with ExeOW achieved HbA1c targets.

ExeOW Compared to Liraglutide

Non-inferiority of ExeOW as compared to the once-daily GLP-1 analogue liraglutide 1.8 mg(LIRA) was tested in a large RCT which used more stringent criteria for non-inferiority than those used in prior non-inferiority studies (upper bound of the 95% CI of the difference in change of HbA1c \0.25% as compared to 0.4%in other ExeOW non-inferiority studies) [17].Both once-daily liraglutide and once-weekly exenatide led to improvements in glycemic control, with greater reductions noted with liraglutide.

Non-Glycemic Effects

Effects on Body Weight

Both exenatide formulations, ExeBID and ExeOW, were demonstrated to be negative regulators of appetite and food intake, and these effects result in an appreciable body weight reduction [18]. The underlying mechanism is complex and is the result of combined actions on different systems including the gastrointestinal and the central nervous systems (CNS). The gastrointestinal effects of GLP-1 and its agonists, including exenatide, are mediated by inhibition of gastrointestinal motility and secretion. They are involved in the ‘‘ileal brake’’ mechanism causing slowdown of progression of food in the gastrointestinal tract with consequent lowering of postprandial blood glucose levels and increased sense of satiety. However, the effects on the gastrointestinal system do not appear to be the main mechanism responsible for body weight decrease during ExeOW therapy.

Effects on Cardiovascular System

In the diabetic population, GLP-1 agonists, including exenatide, have different and peculiar effects on the cardiovascular system, including modification of cardiovascular risk factors,hemodynamic effects on cardiac function, and cardioprotective effects [19].

Cardio protective Effect

Activation of the GLP-1 receptor exerts, at least in vitro, a protective function on cardiomyocytes by increasing glucose uptake and acting on the metabolic pathways of oxidative stress and apoptosis [20]. in addition, preclinical studies suggest that GLP-1 receptors located in the heart and vasculature may play a protective role with respect to cardiovascular disease. The possible use of exenatide in interventional cardiology has been investigated. In a porcine model experimental exenatide reduced ischemic injury in terms of size and deterioration of cardiac function.

Clinical efficacy

Patient Acceptance

Patient satisfaction is an important variable for the acceptance and ultimately for the efficacy of antidiabetic therapies.In a survey aimed at assessing patients’ attitudes toward a once-weekly injectable therapy in patients with chronic illnesses, glucose-lowering medications administered on a weekly basis were viewed positively by patients withT2D [21]. especially those already treated with injections or dissatisfied with their current treatments or outcomes .Patient-related outcomes were prospectively evaluated in one open label RCT comparing ExeOW versus ExeBID and in one double-blind RCT comparing ExeOW versus PIO and SITA. Diabetes treatment satisfaction questionnaire–status and Impact of weight on quality of life lite were assessed in both studies, over 6-month up to 1-year treatment duration. Within the duration-1 study patients in both groups experienced significant and clinically meaningful improvements in treatment satisfaction and QoL which further significantly improved between weeks 30 and 52 for patients switching from ExeBID to ExeOW.

Safety and tolerability

Safety

Over the past years there have been concerns for the long-term safety of incretin-based therapies, specifically as regards their potential to promote rare events such as acute pancreatitis, to initiate histological changes suggesting chronic pancreatitis, including associated preneoplastic lesions, and in the long run even pancreatic cancer. Concerns were also raised as regards a potential increased risk of developing medullary thyroid cancer.

Tolerability

The most common treatment-emergent adverse events reported in RCTs with ExeOW are summarized in The most frequent events associated with ExeOW therapy are gastrointestinal (nausea, vomiting, diarrhea) and injection site reactions (nodules ,pruritus, erythema) [22]. These events occur more frequently in the initial phase of treatment, with incidence decreasing over time as indicated by the analysis of the proportion of patients Reporting selected symptoms over time and further confirmed by the analysis of the annual event rates over a 6-year follow-up within the DURATION-1 study.The overall withdrawal rate in RCTs ranged from patients discontinuing treatment because of an adverse event,mainly due to gastrointestinal side effects Gastrointestinal side effects and withdrawals due to adverse events reported with ExeOW, though generally

more frequent as compared to oral antidiabetic agents or insulin, were markedly lower than with ExeBID or with LIRA [23].

Adverse Reactions

While on study drug, 38 out of 39 patients in the active drug (exenatide ER) group experienced at least one adverse event, while in the placebo group, a total of 28 out of 35 patients (80.0%) experienced at least one adverse event. There was a significant difference between the drug group and the placebo group with respect to gastrointestinal disorders. Skin manifestations were more frequent in the exenatide ER group. However overall, there were no significant differences between the treatment groups in the other organ class adverse event categories nor with respect to grade 3 and grade 4 events.

Current Perspectives

Treatments with exenatide QW showed clinical efficacy and safety and achieved borderline reductions in CVD for patients with T2DM in the above trials. The five- or seven years follow-up studies in the duration-1 trial reported sustained improvements in glycemic control and no unexpected safety findings by treatment with exenatide QW, demonstrating the long-term usefulness of exenatide QW in clinical practice. In addition, once-weekly GLP-1RAs, including exenatide QW, are more convenient, and are therefore preferred by patients and more likely to encourage treatment adherence compared to agents which need daily injection. However, taking the results from the trials of other GLP-1RAs together, exenatide QW might be considered less preferable than other GLP1-RAs for the management of T2DM, especially for patients with high CV risk. The outcomes of trials using GLP-1RAs based on exendin-4 (exenatide QW, lixisenatide and efpeglenatide). The results indicate that, among the GLP1-RAs based on exendin-4, efpeglenatide may be the first choice if it becomes available.

Conclusion

The recent availability of new classes of medications and drug formulations represents an important improvement in the treatment of T2D.

A long-acting formulation of exenatide has been developed foronce-weekly administration by encapsulating exenatide in microspheres of the biodegradable polymer PLG. Although this formulation is new, exenatide and PLG encapsulation have been used clinically for 5 and 25 years, respectively. GLP-1 RAs are now an accepted treatment option for T2DM. They have multiple positive effects on many of the pathophysiological mechanisms in the disease, result in substantial improvements in HbA1c levels and fasting and postprandial blood glucose levels, often result in weight loss in overweight patients, have many other positive nonglycemic effects, and in our opinion, are safe.

This review summarized the current evidence of the clinical efficacy and safety of exenatide OW, and discussed future perspectives on the use of exenatide QW.

Author Contributions

All authors are contributed equally

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Declaration of Competing Interest

The Authors have no Conflicts of Interest to Declare.

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