NEW ORAL oral formulation glucagon-like peptide 1 (GLP1) SEMAGLUTIDE

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Abstract

In recent years, new classes of drugs have entered the market for the treatment of type 2 diabetes mellitus (T2DM) with good efficacy on the normalization of blood glucose and with a reduction in the risk of hypoglycaemia and with significant effects on weight reduction. One of the most promising classes in achieving these goals was that of the agonists (GLP) -1. However, a difficulty in using these drugs arises from subcutaneous administration, a route that is not very convenient for users and with the risk of infections. More recently, a GLP-1 agonist, semaglutide, has been developed which can be administered orally. In this review article, we discussed the effectiveness of GLP-1 agonists, oral semaglutide and its therapeutic potential.

Introduction

The prevalence of type 2 diabetes (T2DM) is on the increase worldwide, tightly linked to enlarging waistlines and the expanding number of individuals who are overweight and obese. T2DM is a metabolic disease commonly characterized by an increase in blood glucose levels, the disease occurs due lack of sensitivity tissue to insulin action. It is important that the disease is diagnosed and managed in advance to prevent or slow down its potential complications other organs such as nephropathy, retinopathy, neuropathy, cardiovascular damnages, diabetic foot disease and ulcer. The pathology of diabetes has a multifactorial character and presents a malfunction of the expression of several genes responsible for the complications of the pathology itself. T2DM is also a socio-economic problem considering the high incidence of the disease, therefore, this has contributed to the creation and development of numerous drug treatments. Today, a number of new classes of drugs used to treat T2DM have been developed and subsequently released on the market that effectively lowers glucose levels minimizing the risk of hypoglycaemia and inducing weight loss.
Among the most promising classes are the Glucagon like peptides GLP-1 agonists. A drawback of GLP-1 receptor agonists is the need for subcutaneous injections, with repercussions on compliance, but a new agent of this class, semaglutide has proven to be effective when administered orally. In this review article, we discuss effects of the analog class GLP-1 with particular attention on oral semaglutide and the potential role of this therapy in people with type 2 diabetes. (1-2-3-4-5-6-7)

Physiology Of GLP-1

GLP-1 is a 30 amino acid peptide hormone (GLP-1 7–36) secreted mainly by cells "L" and "K" of the intestinal tract. The levels of this hormone rise following glucose consumption and, to a lesser extent other nutrients, particularly when food reaches the duodenum. GLP-1 secreted binds to its receptor (GLPR) on pancreatic beta cells and other organs, including the kidney and brain. Its action on beta cells of the pancreas leads to an increase in insulin secretion, mainly due to an increase in cAMP production. One of the main factors influencing the circulating levels of GLP-1 is the dipeptidyl peptidase-4 (DPP-4) enzyme. DPP-4 is known for cutting a wide range of substrates, making them inactive including growth factors, neuropeptides, and vasoactive peptides, also inactive GLP-1 (and other human incretin GIP) quickly and therefore the activity of GLP-1 in non-augmented physiology is relatively short duration (<2 minutes in plasma). For this reason, parenteral administration of GLP-1 in its native form results in rapid inactivation that requires changes to the structure for therapeutic use and prolonged half-life. Outside of the effects on the pancreas, GLP-1 modulates the gastrointestinal tract, where it acts as a potent gastric emptying inhibitor and this leads to a greater feeling of satiety, which helps lose weight. GLP in the brain

regulates the hunger centers and therefore the body weight also highlighting the fundamental role of GLP 1 in the central nervous system. In the cardiovascular system, GLP-1 has been physiologically active and has an effect on the walls of blood vessels and to repair the endothelium from damage to atherosclerotic plaques (8-9-10-11-12-13-14-15-16-17-18-19)

An Overview Of Existing Subcutaneous GLP-1 Receptor Agonists

Exenatide was the first GLP-1RA on the market to receive approval by the FDA in 2005. Numerous other GLP-1s. RA followed either as a daily injection (liraglutide, lixisenatide) or weekly (prolonged-release exenatide, albiglutide, dulaglutide, and semaglutide). The hypoglycaemic effect of these agents is beyond that doubtful with an average reduction in HbA1c ranging from 0.3% 1.2% compared to placebo. This glycemic efficacy is stored regardless of whether it is used as monotherapy or added to a single or combination of hypoglycaemic agents agents. improving and provoking HbA1c levels significant weight loss which makes these agents excellent for the treatment of individuals with T2D.

Exenatide

The medicine is indicated for the treatment of type 2 diabetes mellitus in combination with metformin and / or a sulphonylurea in patients who have not achieved adequate glycemic control with the maximum tolerated dose of these oral therapies. It is administered weekly by subcutaneous injection into the thigh, abdomen or upper part of the arms; 60 minutes before the first and last daily meal with at least 6 hours between the two administrations. The drug can frequently increase the risk of sulphonylurea-induced hypoglycaemia. Other side effects frequently associated with the use of the drug are: nausea,,diarrhea. More rarely it can determine: decreased appetite, asthenia, decrease in body weight, dyspepsia, abdominal pain.

Liraglutide

The use of this drug was approved in 2009 by the EMA (European Medicines Agency) and in 2010 by the FDA for the treatment of T2DM not adequately controlled by metformin, sulphonylureas or thiazolidinediones (alone or in association). Liraglutide represents the second agonist of GLP-1, the other homologue of GLP-1 is the synthetic version of hexendin-4 that is exenatide. Liraglutide has a significant ability to make lose weight and a preparation with single and daily administration for chronic weight treatment has recently been recorded 2015 in Europe. The absorption of liraglutide after subcutaneous injection it is slow and the maximum concentration levels are reached 8-12 hours after administration. The exposure of the drug has been shown to increase proportionally to the dose, for example: following the administration of a single dose of liraglutide 0.6 mg the maximum concentration is 9.4 nmol / L, while after the injection of a single dose of liraglutide 1.8 mg the mean concentration is approximately 34 nmol / L. The absolute bioavailability of liraglutide after subcutaneous administration is approximately 55%. The most common reactions following treatment with liraglutide concern gastrointestinal diseases such as nausea (28%), diarrhea (12%), vomiting (10%), but also constipation and abdominal pain. These kinds of side effects develop more frequently in patients over 70 years of age. However, most of these subside within a few days of starting therapy, which is why it is very well tolerated by patients. Many of the side effects are found when the drug is associated with sulphonylureas to enhance the action of the latter.Less common are: hypoglycaemia, of which there is a very low risk when used in monotherapy. However, it can occur with an uncommon frequency when associated with a sulphonylurea. cholecystitis, develops in rare cases (0.1%) pancreatitis, few cases (0.4%) headache, often when associated with a sulphonylurea. (20-21-22-23-24)

Lixisenatide

Lixisenatide is a once-daily injectable GLP-1 receptor agonist for the treatment of T2DM Lixisenatide is used as adjunct to diet and exercise to treat diabetes type II, about 0.1% of cases people have had anaphylactic reactions to lixisenatide and in about 0.2% of cases the drug has caused pancreatitis. Use with insulin or sulfonylurea may cause hypoglycemia. In some cases, people with no kidney disease have had acute kidney injury and in some people with existing kidney disease the condition has gotten worse. Because lixisenatide is a peptide people can and do develop an immune response to it that will eventually make the drug ineffective; people who have developed antibodies to lixisenatide tend to have more inflammation at the injection site.
At least 5% of people had nausea, vomiting, diarrhea, headache, or dizziness

Dulaglutide

It can be used once weekly. The FDA approved dulaglutide for use in the United States in September 2014. The compound is indicated for adults with type 2 diabetes mellitus as an adjunct to diet and exercise to improve glycemic control. Dulaglutide is not indicated in the treatment of subjects with type 1 diabetes mellitus or patients with diabetic ketoacidosis because these problems are the result of the islet cells being unable to produce insulin and one of the actions of dulaglutide is to stimulate functioning islet cell to produce more insulin. Dulaglutide can be used either stand-alone or in combination with other medicines for type 2 diabetes, in particular metformin, sulfonylureas, thiazolidinediones, and insulin taken concomitantly with meals. The most common side effects include gastrointestinal disorders, such as dyspepsia, decreased appetite, nausea, vomiting, abdominal pain, diarrhea. Some patients may experience serious adverse reactions: acute pancreatitis (symptoms include persistent severe abdominal pain, sometimes radiating to the back and accompanied by vomiting), hypoglycemia, renal impairment (which may sometimes require hemodialysis). The risk of hypoglycemia is increased if the drug is used in combination with sulfonylureas or insulin.

Semaglutide subcutaneous injection

Semaglutide is a medication for the treatment of type 2 diabetes. Side effects include medullary thyroid cancer, kidney problems, diabetic retinopathy, allergic reactions, low blood sugar, and pancreatitis. Semaglutide acts like human glucagon-like peptide-1 (GLP-1) so that it increases insulin secretion, thereby increasing sugar metabolism. It is distributed as a metered subcutaneous injection in a prefilled pen. One of its advantages over other antidiabetic drugs is that it has a long duration of action, thus, only once-a-week injection is sufficient. An injection version was approved in 2017 in the United States, and in Europe, Canada, and Japan in 2018.

Oral Semaglutide

A version which is taken by mouth (Rybelsus) was approved in 2019 in the United States. It is the first glucagon-like peptide (GLP-1) receptor protein treatment approved for use in the United States that does not need to be injected. Before this approval, patients did not have an oral GLP1 option to treat their type 2 diabetes, and now patients will have a new option for treating type 2 diabetes without injections.Like GLP-1, Rybelsus slows digestion, prevents the liver from making too much sugar, and helps the pancreas produce more insulin when needed. The efficacy and safety of Rybelsus in reducing blood sugar in patients with type 2 diabetes were studied in several clinical trials, two of which were placebo-controlled and several of which were compared to other GLP-1 injection treatments. Rybelsus was studied as a stand-alone therapy and in combination with other diabetes treatments, including metformin, sulfonylureas (insulin secretagogues), sodium-glucose

co-transporter-2 (SGLT-2) inhibitors, insulins and thiazolidinediones, all in patients with type 2 diabetes. In the placebo-controlled studies, Rybelsus as a stand-alone therapy resulted in a significant reduction in blood sugar (hemoglobin A1c) compared with placebo, as determined through HbA1c tests, which measure average levels of blood sugar over time. After 26 weeks, 69% of those taking 7 mg once daily and 77% of those taking 14 mg once daily of Rybelsus decreased their HbA1c to lower than 7%, compared with 31% of patients on placebo. Rybelsus is not for use in patients with type 1 diabetes and people with diabetic ketoacidosis. Rybelsus also has warnings about pancreatitis (inflammation of the pancreas), diabetic retinopathy (damage to the eye's retina), hypoglycemia (low blood sugar), acute kidney injury and hypersensitivity reactions. It is not known whether Rybelsus can be used by patients who have had pancreatitis. The risk of hypoglycemia increased when Rybelsus was used in combination with sulfonylureas or insulin. Rybelsus should be taken at least 30 minutes before the first food, beverage or other oral medication of the day, with no more than 4 ounces of plain water. Rybelsus slows digestion, so patients should discuss other medications they are taking with their health care provider before starting. The most common side effects are nausea, diarrhea, vomiting, decreased appetite, indigestion and constipation. Semaglutide is a peptide drug, which consists of 31 amino acid residues and is very similar to native GLP-1 with only three minor structural differences. Alanine amino acid at position 8 is substituted with α-aminoisobutyric acid, which makes the molecule more resistant to the degradation by DPP-4. A spacer is placed to conjugate a C18 fatty diacid to the position 26 lysine improving albumin-binding properties; consequently, this prolongs plasma half-life and reduces renal clearance of the drug Further modification in the tablet version of the medication includes addition of a permeation enhancer N-(8-[2-hydroxybenzoyl] amino) caprylic acid (SNAC, Eligen® Technology, Emisphere Technologies). SNAC is a small fatty acid derivative that acts on transcellular pathways, increases pH locally, and accelerates the absorption of molecules (in this case semaglutide) across the gastric epithelium avoiding the activation of proteolytic enzymes and pH-induced degradation in the stomach. In this fusion the combination of semaglutide and SNAC can overcome the limited permeability of the gastrointestinal tract, low gastric pH, and the rapid gastric breakdown of proteins and peptide drugs.

Safety and tolerability

Oral semaglutide appears to be safe and generally well tolerated with a profile similar to other GLP-1 receptor agonists. Through phase 3 clinical trials, they registered mild or moderate nausea (5-21% of participants). In the phase 2 study, participants who started with a lower dose fewer episodes of nausea have been reported; There have been very few hypoglycaemic episodes and percentages they were similar in the semaglutide and placebo groups. A total of 6–12% of people treated with oral semaglutide performed discontinuation of treatment due to adverse events compared to three cases of pancreatitis were confirmed in the participants receive oral semaglutide.

Hepatic impairment

Individuals with T2DM have an increased risk of developing hepatic impairment, which can affect PK properties of drugs .PK, safety, and tolerability of once-daily oral semaglutide were investigated in 56 individuals with normal or reduced liver function. Child-Pugh criteria were used to categorize hepatic impairment as mild (Child-Pugh Grade A; 5–6 points), moderate (Child-Pugh Grade B; 7–9 points), or severe (Child-PughGrade C; 10–15 points). Hepatic function did not affect the primary and secondary end-points of the study after the tenth dose In addition, no safety concerns were identified and observed adverse events (headache, dyspepsia, vomiting, decreased appetite, and diarrhea) were similar to those reported for other approved members of the class.

Renal impairment

The drug has also been studied in patients with impaired renal function which could affect it PK, safety and tolerability of oral semaglutide, 60 individuals with normal or reduced kidney function have been studied. The estimated creatinine clearance was used to classify the deterioration such as: mild (60–89 ml / min / 1.73 m2), moderate (30–59 ml / min / 1.73 m2) and severe (15–29 ml / min / 1.73 m2). The study showed that it has gone down kidney function did not affect oral exposure of semaglutide, half-life or PK. The adverse events reported were in line with those commonly found with GLP-1 receptor agonists: vomiting, headache and nausea. There have been rare cases of hypoglycaemia.

Drug interactions

Due to the potential delay in gastric emptying and SNAC Guided absorption potentiation has been hypothesized as oral semaglutide could alter the PK of concomitant administration oral medications, therefore, several single sequence crossovers studies have been conducted to investigate the effects of oral therapy semaglutide on metformin, digoxin, lisinopril, warfarin, furosemide, rosuvastatine and omeprazolo.
With metformin and digoxin, A total of 32 healthy was studied the study demonstrated that oral semaglutide increased the area under the plasma drug concentration- time curve (AUC) but did not change the peak plasma concentration (Cmax) of metformin The AUC and Cmax of digoxin were unaffected.
With lisinopril and warfarin, A total of 46 healthy was studied to investigate effects of oral semaglutide on the PK of lisinopril and warfarin The study demonstrated that oral semaglutide had no effect on lisinopril and warfarin exposure and half-life and also did not change the international normalized ratio response to warfarin.
With furosemide and rosuvastatin, In-vitro experiments indicated that SNAC could inhibit furosemide and rosuvastatin transporters and potentially result in elevated plasma levels of these drugs, thus, a total of 41 healthy was studied individuals to investigate the effects of oral semaglutide and SNAC alone on the PK of furosemide and rosuvastatin. The trial investigators concluded that SNAC did not inhibit furosemide (OAT1/3) and rosuvastatin (BCRP/ OATP1B1) transporters and there were no clinically relevant increases in the exposure of these drugs when coadministered with oral semaglutide.
With omeprazole, The SNAC improves the absorption of oral semaglutide in a pH dependent way. Drugs that alter gastric pH could potentially influence SNAC and consequently affect exposure to semaglutide. Proton pump inhibitors are frequently prescribed in T2DM. The mechanism of action of this class involves the inhibition of gastric acid secretion and therefore increase in pH by blocking the H, K-ATPase in the stomach. Was essential to investigate whether the co-administration of the proton pump inhibitors with oral semaglutide could alter the PK properties of the latter. studies carried out suggest that the Oral semaglutide therapy with omeprazole probably will not request any dose adjustments. uently affect exposure to semaglutide. inhibitors with oral semaglutide probably will not request any dose adjustments.

Pharmacocinetics aspects

The short half-life of human GLP-1 resulting from degradation by DPP-4 has raised a challenge for pharmaceutical form of the oral semaglutide.
Reversible binding to albumin by using fatty acid derivatization is one approach to protect GLP-1RA from early degradation in plasma by DPP IV. Long-chain fatty acid derivatization and specific positions of amino acid substitution prevent the peptide from DPP-4 degradation and renal filtration resulting in a prolonged half-life for semaglutide (165 hrs) after a single injection. The challenge

to develop an oral preparation for semaglutide ascribes by a hydrophilic, macromolecular peptide is naturally susceptible to low pH and gastric/intestinal enzymes, as well as poor gastrointestinal absorption. The Salcaprozate sodium (SNAC) is an intestinal permeation enhancer. the use of SNAC to increase oral bioavailability of several peptide hormones has been proven, including salmon calcitonin, parathyroid hormone, GLP- 1RA, and peptide YY. Importantly, SNAC has been granted a safe status by the FDA for the use with vitamin B12. The pharmacokinetics study of oral semaglutide in healthy and T2D subjects showed that, at steady state, the half-life of oral semaglutide co-formulated with 300 mg SNAC was approximately 160 hrs.. The SNAC prevent gastric degradation by neutralizing a low pH microenvironment surrounding the tablet, resulting in an increased concentration-dependentflux of semaglutide across the gastric mucos.

Comparisons Of Oral Semaglutide And Injectable Liraglutide

To determine the efficacy and safety of oral semaglutide such as monotherapy the PIONEER-1 study demonstrated oral glycemic superiority once a day semaglutide versus placebo in 703 adults with T2D . 7 mg and 14 mg of oral semaglutide significantly reduced HbA1c from baseline by −0.9%, −1.2% e-1.4%, respectively, compared to -0.3% in placebo group. In addition, the three doses of oral semaglutide it also provided a superior reduction in body weight a −1.5 kg, −2.3 kg and −3.7 kg, respectively, compared -1.4 kg in the placebo group. The overall incidence of adverse events and serious adverse events included hypoglycaemia was similar for both oral and semaglutide placebo; however, the 7 mg and 14 mg of oral semaglutide it predominantly showed higher premature termination rates due to gastrointestinal complaints. A more important question is whether oral preparation semaglutide is as effective as injectable preparations by GLP-1RA. To answer this question, studies comparison between oral semaglutide and subcutaneous liraglutide o semaglutide was conducted. The sudy PIONEER-4 directly compared the glycemic effects and body weight reduction of once a day oral semaglutide and once a day subcutaneous liraglutide among 711 T2D participants. At 26 weeks, the study showed that oral semaglutide and liraglutide decreased HBA1c by 1.2% and 1.1% respectively, indicating that oral semaglutide has similar glycemic levels effectiveness at well-established liraglutide injections. Additionally, oral semaglutide resulted in superior weight loss (−4.4 kg) compared to liraglutide (−3.1 kg; $p < 0.01$). However, adverse events leading to early suspension of the study drug were moderately higher in oral semaglutide (11%) compared to liraglutide (9%). (25-26-27-28-29-30-31-32-33-34-35)

Analisi cost efffectiveness

Based on long term clinical projections and cost results, oral semaglutide 14 mg offers more advantageous treatment option than others treatments for T2DM, including empagliflozin, sitagliptin and liraglutide. Clinical benefits are the result of a reduced incidence e delay in the onset of long-term diabetes complications with oral semaglutide. Offering patients the benefits of a GLP-1 receptor agonist in a once-daily tablet could overcome some of the obstacles that lead to therapeutic inertia, as evidence suggests that patient concerns over potential side effects of therapies, including hypoglycaemia and weight gain, as well as fear of injections, often lead to delayed intensification of treatment, despite poor glycaemic control. The complications related to diabetes were minor oral semaglutide 14 mg, which produced a cost savings that partially offset his higher treatment costs against empagliflozin and sitagliptin. Oral semaglutide has been associated with inferior treatment costs against liraglutide, with additional costs savings obtained through a reduced incidence of complications related to diabetes. (36-37-38-39-40-41-42-43-44-45)

CONCLUSION

Oral semaglutide has already proven to be effective to lower glucose levels and is generally well tolerated, from the first results of the pre-registration tests, however the tolerability and safety

profile needs further data that will arise from postmarketing pharmacovigilance. Certainly the drug aims to be a very valid therapeutic alternative in the treatment of T2DM, with an advantage in terms of compliance for the patient user, who can comfortably take the drug orally without resorting to injections, especially in patients with fear of injection. Therefore, oral semaglutide can reasonably be considered as another drug in the GLP-1RA class for the treatment of T2D patients. The use of oral semaglutide should be considered as a second line treatment after the metformin, especially when the weight is a problem and possibly in those with higher cardiovascular levels risk. Another advantage is that the drug has not shown drug interactions with the most common drugs used by a diabetic patient, and has not shown substantial pharmacokinetic changes in patients with renal or hepatic insufficiency Furthermore, very importantly, the drug has been shown not to cause an increased risk of hypoglycaemia, in line with the other drugs of the same class administered by injection. Oral semaglutide was projected to be a cost-effective treatment option versus empagliflozin, sitagliptin and liraglutide for the treatment of patients with type 2 diabetes in the UK. With the addition. Oral semaglutide is an important step forward by offering a oral hypoglycaemic therapy that effectively reduces glucose levels avoiding hypoglycemia and having positive effects on weight and cardiovascular risk. During clinical development, oral semaglutide formulation with 300 mg of SNAC it did not trigger any unexpected safety signals.

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