Oral GLP1 Analog: Where Does the Tide Go?

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ABSTRACT: T2D is a potentially preventable disease that has been ranked the seventh leading cause of mortality in the United States. There is strong evidence demonstrating that preventing type 2 diabetes is, in many cases, attainable through lifestyle intervention. Unfortunately, prediabetes is mostly overlooked and awareness with diabetes prevention tools is lacking among primary care physicians. Nationally, efforts were not successful in reversing this epidemic even with an array of diabetes medications. Among the most effective medications for T2D are glucagon-like peptide-1 receptor agonists (GLP-1 RAs), which have been shown to reduce both A1C and body weight. Dulaglutide, liraglutide and injectable semaglutide also reduced cardiovascular events and cardiovascular mortality in patients with established cardiovascular disease or multiple cardiovascular risk factors. In this review, we will examine the first FDA approved oral GLP-1 RA; semaglutide. Moreover, this review will discuss the potential impact oral semaglutide may have on glycemic control, weight loss and cardiovascular comorbidities. It also examines the factors that may impact patient compliance, including cost, side effects and clinical issues. Finally, it deliberates the optimism surrounding the development of oral semaglutide in the treatment of diabetes as well as related conditions, such as obesity and non-alcoholic fatty liver disease (NAFLD).

KEYWORDS: GLP-1 analog, semaglutide, oral GLP-1, T2D

Introduction

Type 2 diabetes (T2D) is a potentially preventable disease that has been ranked the seventh leading cause of mortality in the United States.[1,2] There is strong evidence demonstrating that preventing type 2 diabetes is, in many cases, attainable through lifestyle intervention. Unfortunately, prediabetes is mostly overlooked and awareness with diabetes prevention tools is lacking among primary care physicians.[3,4] Diagnoses of T2D often arise in patients who are overweight or obese and have adopted sedentary lifestyle and consume a disproportionate amount of sugar and fat in their diets.[3] While some patients with T2D are able to change their eating habits and increase physical activity, most patients cannot and have to be treated with antihyperglycemic medications. The well-accepted first-line therapy for T2D is metformin.[4] Metformin alone often is not enough to treat most cases of T2D and a second medication is frequently needed. Among second-line therapies are glucagon-like peptide-1 receptor agonists (GLP-1 RAs).[5] The first GLP-1 RA, exenatide, was approved in June, 2005. In the United States, 6 GLP-1 RAs are currently available. They are: the short-acting formulations exenatide and lixisenatide and the long-acting formulations liraglutide, once weekly extended release exenatide, dulaglutide and semaglutide.[5] The 6 GLP-1 RAs available in the US differ by molecular structure and size, duration of action, pharmacokinetics, ability to penetrate different tissue compartments, dosing intervals, A1C lowering abilities, different effects on the glucose profile and frequency of adverse effects.[6] GLP-1 RAs are widely associated with increased satiety, weight loss and delayed gastric emptying, as well as a decrease in A1C and severity of hypoglycemic incidents.[5]

The US Food and Drug Administration (FDA) has recently approved semaglutide (Rybelsus®, Novo-Nordisk, Denmark) as the first and only GLP-1 analog for adults with T2D. The approval was granted for its 7 mg and 14 mg tablets. The approval indicates semaglutide as an adjunct therapy to diet and exercise to improve glycemic control in patients with T2D who are not achieving their A1C goals with other antihyperglycemic medications. The approval of semaglutide was based on results of 10 clinical trials under the PIONEER program—a series of head-to-head trials comparing this GLP-1 agonist versus sitagliptin, empagliflozin, and liraglutide 1.8 mg in 9543 patients with T2D.[7] These clinical trials showed that semaglutide significantly reduced A1C and body weight. Common adverse reactions including nausea, abdominal pain, diarrhea, decreased appetite, vomiting, and constipation were reported in ⩾5% of patients in these clinical trials.[7,8]

Mechanism of Action of GLP-1

Following food consumption, gastrointestinal tract (GIT) naturally releases several hormones; collectively called incretins. GLP-1 is one of the incretins family that stimulates pancreatic β-cells to secrete insulin.[9] GLP-1 hormone is secreted from L-cells of the small intestine.[10] GLP-1 Receptors (GLP-1 Rs) are mainly expressed in the pancreas, bowels and the central nervous system. They are, less abundantly, found in heart, lungs, kidneys, vasculature and peripheral nervous system. GLP-1 Rs target the hormonal and peptide signaling pathways between the brain and the gastrointestinal track in order to restore sensitivity of pancreatic β-cells and regulate physiologic insulin secretion.[11] Specifically, GLP-1 binds to GLP-1 Rs, which stimulate activation of adenyl cyclase. Consequently, this

sequence causes cylic adenosine mono phosphate (cAMP) levels to rise. Increased cAMP levels activate protein kinase A (PKA) and cAMP regulates guanine nucleotide exchange factor 2 (Epac2) thus producing a signal for increased insulin secretion.[12] This mechanism is important for treating T2D, which is characterized by insulin deficiency that result in chronic and progressive hyperglycemia.[13] Sustained hyperglycemia without intervention increases risks of macro- and microvascular complications, which may ultimately lead to chronic morbidity or death.[13,14] GLP-1 RAs are commonly indicated for patients who have had sustained hyperglycemia despite treatment with other antihyperglycemic medications, especially for patients who are overweight or obese and have a previous history of cardiovascular disease or with multiple risk factors for cardiovascular disease.[15]

GLP-1 RAs exercise 2 major functions that contribute to their antihyperglycemic effects. First, they enhanced β-cell function and second they simultaneously suppress inappropriately high glucagon secretion from pancreatic α-cells. They also delay gastric emptying and increase satiety, thus helping weight loss.[16,17] Remarkably, high levels of glycemic control and weight loss are achieved without conferring risk of hypoglycemia, which makes GLP-1 RAs superior to other antihyperglycemic drugs that some of them may cause hypoglycemia.[18] These medications also have potential cardiovascular benefits in patients with T2D and established cardiovascular disease or with multiple risk factors for cardiovascular disease.[19] However, this benefit was only shown with liraglutide, injectable semaglutide and dulaglutide long-term use.[20-23] All other GLP-1 RAs showed no increase in major adverse cardiovascular events; including cardiovascular death, non-fatal myocardial infarction, non-fatal stroke versus comparators.[21-23] GLP-1 RAs usually decrease systolic blood pressure (SBP) and, to a lesser extent, diastolic blood pressure (DBP), which is a major cardiovascular risk factor.[24] They may also improve lipid profile, which is another major cardiovascular risk factor.[25]

According to the American Diabetes Association (ADA) and American Association of Clinical Endocrinologists (AACE) diabetes treatment algorithms, GLP-1 RAs are recommended as add-on second-line therapy for patients who do not achieve their A1C target after 3 months of metformin therapy, especially if patients have a previous history of cardiovascular disease. GLP-1 RAs are recommended as first-line therapy in patients who cannot tolerate or have contraindication to metformin use.[26,27]

GLP-1 RA Adverse Events

GI intolerance is the most common adverse effect in GLP-1 RAs therapy. This includes nausea (25-60%), vomiting (5-15%) and diarrhea (10-20%). However, these symptoms are mostly mild, transient and dose-dependent. They can be reduced to some extent if the therapy is introduced using a gradual dose-escalation strategy. The most common adverse events are nausea and vomiting, both of which, are usually transient and of mild or moderate severity. Patients usually develop tolerance to these adverse effects over time.[15] Although pancreatitis may occur as a serious side event, concerns regarding pancreatic carcinoma is not proven due to absence of plausible mechanisms and lack of data to support its possibility from randomized controlled trials.[28,29] Similarly, the increased incidence of C-cell hyperplasia and medullary thyroid carcinoma, which was noticed in rodent studies, but was not replicated in large scale human studies with the careful monitoring of serum calcitonin levels.[30] GLP-1 RAs are also associated with an increase in heart rate by 2 to 3 beats per minute.[31] Injection-site reactions have been described with GLP-1 RAs, however it is difficult to compare their incidence between different GLP-1 RAs, as data are limited.[20] The adverse effects events are generally dependent on the pharmacokinetic profile of a GLP-1 RA used, with higher incidence of GI events after short acting agents and more chronotropic effects by longer acting ones.[32]

Oral Semaglutide

GLP-1 RAs were originally developed and offered in injection form. Oral GLP-1 RA is a modified version from its subcutaneously administered semaglutide. Semaglutide has a 94% homology with human GLP-1.[16] Minor modifications were made in an effort to extend its bioavailability to be administered once-weekly, since natural human GLP-1 hormone is biodegraded in less than 2 minutes.[33]

Converting a GLP-1 RA into a pill form was cumbersome, since digestion and absorption of an active compound is more complex, where it has to withstand the stomach acidity and penetrate intestinal structures with low permeability, while maintaining a consistency that can eventually be circulated into the body.[17] Although there are many ways to enable drug absorption, the most successful one is to directly modify the molecule structure and integrate an absorption enhancer.[34] Semaglutide was fused with a carrier, sodium N-(8-[2-hydroxybenzoyl] amino) caprylate (SNAC). SNAC provides enough GLP-1 durability to be properly absorbed in the stomach and ultimately enables drug circulation into the blood.[17] Moreover, SNAC facilitates semaglutide absorption across the gastric epithelium, while protecting it from proteolytic degradation. SNAC achieves this through increasing localized pH levels, inducing monomers, and causing a pepsin-inhibiting effect in the stomach.[35] There is 300 mg of SNAC in each oral semaglutide tablet.[36]

Efficacy of Oral Semaglutide

Oral semaglutide was tested in a series of clinical trials focusing on safety and efficacy in head-to-head comparisons with other medications and with other GLP-1 RAs. Primarily, the trials proved that oral semaglutide can successfully function similar to subcutaneous semaglutide. A phase 2, randomized, parallel-group, dose-finding, 26-week trial was conducted comparing oral semaglutide with subcutaneous semaglutide and a placebo. In this trial, 632 participants were randomized to either of the

3 arms. These 3 arms were divided into sub-groups dependent on differing dosage treatments. The oral semaglutide group was divided into 5 subgroups with doses being 2.5, 5, 10, 20, and 40 mg. It is important to note that the FDA approved oral semaglutide in a 14 mg dose, which is much less than the 20 or 40 mg groups tried in the study.[29,37] Furthermore, the oral placebo group received a once-daily dose with dose escalation after 4 weeks, and the subcutaneous semaglutide group received 1-mg dose once-weekly. A1C was measured at baseline and after the 26 weeks of intervention. A1C decreased significantly in the oral semaglutide arm (dose-dependent range, –0.7% to –1.9%, P = .01 for 2.5 mg, P < .001 for all other doses) and subcutaneous semaglutide (–1.9%, P < .001). There was a slight non-significant decrease in A1C in the placebo group (–0.3%). Oral semaglutide demonstrated preeminence over the placebo in achieving glycemic control. Participants on oral semaglutide reduced their A1C by 1.9% compared with 0.3% with placebo (P < .001). Weight loss was greater in participants taking oral semaglutide (dosage-dependent range, –2.1 kg to –6.9 kg) and subcutaneous semaglutide (–6.4 kg) versus placebo (–1.2 kg). The most common adverse effect was nausea. Nausea was reported less frequently in participants who started on lower doses. Gastrointestinal side effects were more prevalent in oral semaglutide arm (31-77%) and subcutaneous semaglutide arm (54%) in comparison to placebo (28%).[29] While this trial is noteworthy, the results are reflective of a higher dose of oral semaglutide than the dose approved by the FDA.

In addition, the trials demonstrated the antihyperglycemic efficacy of oral semaglutide in comparison to another GLP1-RA. In the PIONEER 4, randomized, double-blind, phase 3a trial, oral semaglutide was compared to liraglutide and a placebo. The study included 711 participants, who were randomly assigned to either of the 3. Oral semaglutide was non-inferior in lowering A1C to subcutaneous liraglutide and superior in lowering A1C in comparison to placebo (P < .0001). Although superiority of oral semaglutide in lowering A1C over liraglutide was not established, oral semaglutide was superior effective in lowering body weight (–4.4 kg) than liraglutide (–3.1 kg, P = .0003) and placebo (–0.5 kg, P < .0001). The most common causes of discontinuation of oral semaglutide and liraglutide in this trial were gastrointestinal side effects. Participants experienced mainly nausea, diarrhea or vomiting with 44% of these participants in the oral semglutide group, 34% in the liraglutide group and 14% in the placebo group. Oral semaglutide and liraglutide performed similarly in safety and tolerability parameters.[38]

Finally, since 97.5% of patients with T2D have at least one other comorbid condition, the PIONEER trials demonstrated safety of oral semaglutide among patients with common diabetes comorbidities, namely hypertension, kidney disease and cardiovascular disease. It is estimated that 82.1% of patients with T2D have hypertension, about 24.1% of them have chronic kidney disease and 21.6% develop cardiovascular disease (CV).[39] As part of the PIONEER 6, event-driven, randomized,

double-blind, placebo-controlled trial, oral semaglutide was examined for cardiovascular safety. Patients were eligible to enroll if they had previously been diagnosed with cardiovascular disease or chronic kidney disease, or if they were 60 years of age or older with multiple cardiovascular risk factors. Patients were randomly assigned to receive oral semaglutide or a placebo. Fatal cardiovascular events occurred in 0.9% of patients taking oral semaglutide in comparison to 1.9% of patients in the placebo group. Thus, oral semaglutide was established as noninferior to placebo in terms of cardiovascular safety, with a point estimate analogous to a difference in risk of 21% (P < .001 for noninferiority; P = .17 for superiority). Cardiovascular deaths occurred in 15 of 1591 patients (0.9%) in the oral semaglutide group and 30 of 1592 (1.9%) in the placebo group (P < .001 for noninferiority, P = .17 for superiority). A CV risk reduction with oral semaglutide versus placebo was not demonstrated tested in this trial. This is important to note, since in previous CV outcome trials subcutaneous dulaglutide, liraglutide and semaglutide have shown CDV risk reduction when compared to placebo.[40] Moreover, since cardiovascular disease remains the leading cause of death among patients with T2DM, this information is vital for physicians determining patients' way of management.[22,41]

SGLT2i versus Oral Semaglutide

Sodium-glucose transport protein 2 (SGLT2) inhibitors are also approved as second-line therapy for the management of T2DM. These drugs, like GLP1-RAs, have A1C lowering capabilities. Canagliflozin was the first SGLT2i to receive FDA approval (March 2013). Canagliflozin and other SGLT2i, namely dapagliflozin, empagliflozin, and ertugliflozin, manage T2DM through increasing glucose excretion in urine.[42]

In a randomized, placebo-controlled study looking at canagliflozin as a treatment for T2DM, patients were given 100 mg and 300 mg (the maximum approved dose) of the drug once daily. A1C decreased by –0.38% and –0.47%, respectively, and body weight was reduced by –1.6% and –1.9%, respectively.[43]

In another trial comparing Canagliflozin to subcutaneous semaglutide as an add-on to metformin, patients were given 1 mg of injectable semaglutide or 300 mg of canagliflozin. Patients in the semaglutide group had significantly greater reductions in A1C and body weight than patients receiving canagliflozin (A1C estimated treatment difference [ETD] was –0.49 percentage points (95% CI –0.65 to –0.33; –5.34 mmol/mol, 95% CI –7.10 to –3.57; P < .0001; and bodyweight ETD –1.06 kg, 95% CI –1.76 to –0.36; P = .0029).[44]

In 2015, empagliflozin demonstrated CVD benefits in the form of reducing cardiovascular events and mortality in patients with T2DM and established cardiovascular disease. The drug showed 38% relative risk reduction in CV death (hazard ratio [HR], 0.62; 95% confidence interval [CI], 0.49–0.77; P < .001). There was a similar finding for canagliflozin in a cardiovascular assessment study. The primary endpoints were death from cardiovascular causes, non-fatal MI, or non-fatal stroke. These

endpoints were significantly lower with canagliflozin than with placebo (26.9 vs 31.5 participants per 1000 patient-years; HR 0.86; 95% CI, 0.75–0.97; *P* < .001 for noninferiority; *P* = .02 for superiority).[45]

There has never been a head-to-head comparison of SGLT2i and oral semaglutide. However, this would be an interesting avenue for research, as both medications can achieve similar treatment milestones for patients with T2DM and they are both offered in pill form. While oral semaglutide might be more effective in reducing A1C and body weight, it was not tested for cardiovascular benefits as canagliflozin and empagliflozin have been.[42]

Convenience of Oral Semaglutide Use

Patient adherence to oral semaglutide depends on several factors. Among the most prominent considerations are drug cost, clinical indications for drug use, and side effects. Broadly speaking, patients with T2D have low rate of medication compliance. Although there is little research to explain the reasons, it is known that patients with T2D generally prefer oral medications over subcutaneous injections.[46] Oral drug delivery is easier to manage, quicker to use and painless. Thus, oral semaglutide has some advantage over comparable injectable GLP1-RAs. Additionally, diabetes is a costly disease, where patients with diabetes spend approximately 2.3 times more money on medical services than those without diabetes.[47] This may explain why a large portion of patients with diabetes stop filling their prescriptions.[48] Oral semaglutide is available at a competitive price. The cost of a 30-day supply of oral semaglutide is approximately $772 in comparison to injectable liraglutide, which is around $886 (Table 1).[49]

In general, medication adherence is partly dependent on how it is taken and the convenience of its administration. Oral semaglutide should be taken at least 30 minutes before eating and with no more than 4 ounces of water,[50] which is relatively inconvenient for few patients. Other GLP-1 RAs are taken by subcutaneous injection, either twice daily, once daily or once weekly. All subcutaneous injections necessitate a sterile environment (alcohol swab).[51] There is more logistical flexibly in taking subcutaneous GLP-1 RAs, but we cannot ignore the psychological burden of taking an injection. The perception of an injection may hold greater negativity than the logistical requirements of oral medication. However, few patients may prefer once weekly injection over daily oral or injectable medications.

The side effects of the GLP-1 RAs arguably play the largest role in drug compliance. A survey conducted among 10 987 patients from the European Union and the United States who were taking GLP-1 therapies, found that the most common phrases that patients say as reasons for discontinuation of GLP-1 RAs were "it made me feel sick" (64.4% of patients), "made me throw up" (45.4% of patients) and "prefer oral medication over injections" (39.7% of patients).[52] The frequency of GI side effects that were shown with GLP1-RAs remained constant with oral GLP-1 RA. It is possible that GI side effects may attenuate patient compliance to oral semaglutide, especially when coupled with the inconvenience of talking it on an empty stomach 30 minutes before eating. However, we should be reminded that the third most prominent reason for GLP-1 RAs discontinuation was "prefer oral medication over injections", which may give some advantage to oral semaglutide over other injectable GLP-1 RAs. Post marketing studies may confirm or deny these assumptions.

Subscriber and Insurance Attitude

Patient insurance coverage for oral semaglutide dependents on insurance plans or prescription benefits plan held by the patient. Generally, the cost is highly variable. We know from previous comparison analyses that the coverage for diabetes by federal and state healthcare insurance is lacking in contrast to coverage by most private health insurance.[53] This is likely not the only disadvantage that patients with public healthcare insurance may face in trying to gain access to an expensive drug like oral semaglutide. In a national survey of 2704 adults with self-reported diabetes, the statistics of insurance coverage showed that patients without coverage were 6 times more likely to discontinue their diabetes treatments because of cost, than insured patients. For patients covered by public health insurance plans, a large majority required supplemental insurance to obtain additional coverage for diabetes treatments.[53] Additionally, most Medicare plans have a coverage gap, which is termed "donut hole." The donut hole is when patients and their insurance plans have spent a certain amount of money for covered drugs and beyond it patients became responsible for paying all remaining costs out of pocket for the rest of the year. Once patients reach their yearly limit, the drug coverage kicks back in.[54] This phenomenon likely deters patients from trying or staying on expensive branded medications for diabetes. It is to be expected that patients trying a new or novel diabetes medication like oral semaglutide should have an insurance coverage for it.

Risks of Off-Label Use outside the United States

In countries that are not stringent in proper use of medication as the US does, it is likely that oral semaglutide will be introduced to few patients as an obesity drug. While oral semaglutide has been shown to enhance weight loss, it has not been studied strictly for this indication or been approved by the FDA for obesity indication. The common practice of using medications for non-approved purposes; referred to as "off-label" drug prescription, exists in the United States but is far more common in countries without stringent pharmaceutical regulations.[55,56]

Use of medications "off-label" becomes more serious when patients receive or take medications without adequate medical supervision or proper guidance. For example, patients may start a medication using an inappropriate high dose. In the case of oral semaglutide, starting at a high dose may increase risk of

Table 1. Comparisons of GLP-1 RAs.[8,49,64-69,70-73]

GLP-1 ANALOG	DATE OF FDA APPROVAL	DOSE	ROUTE OF ADMINISTRATION	MEDIAN NADAC	A1C % DECREASE	KG WEIGHT LOSS
Oral Semaglutide	September 20, 2019	14 mg	Oral	$772	1.4	4.7 to 5.0 kg
Semaglutide	December 5, 2017	1.0 mg	Subcutaneous	$745	1.9	6.4 kg
Liraglutide	January 25, 2010	1.8 mg	Subcutaneous	$886	0.9 to 1.1	3.1 to 3.2 kg
Dulaglutide	September 18, 2014	1.5 mg	Subcutaneous	$730	1.4	3.0 kg
Exenatide	April 28, 2005	2 mg	Subcutaneous	$730	1.38	1.51 kg

Abbreviations: FDA, The Food and Drug Administration; NADAC, National Average Drug Acquisition Cost.

drug intolerance and side events.[51] Additionally, medication may cause serious health problems like pancreatitis. The manufacturer states "It is not known if oral semaglutide can be used in people who have had pancreatitis." Patients who have a history of pancreatitis should be mindful when taking a drug that may potentially cause acute pancreatitis or exacerbate chronic pancreatitis, a message that may be lost without medical supervision or consultation.

Future Directions of Oral GLP-1 RA

Research has shown that GLP-1 therapies may be valuable for treatment of non-alcoholic fatty liver disease (NAFLD) and obesity.[57] Clinical trials are underway in testing oral semaglutide alone or in combination with other medications developed to treat NAFLD.[58] It is also in clinical trial for obesity [https://clinicaltrials.gov/ct2/show/NCT03919929?term=rybelsus&cond=NAFLD&draw=2&rank=1].

NAFLD is a common liver disease and particularly exists in higher frequency in patients with T2D.[59] It eventually leads, in many patients, to Non-Alcoholic SteatoHepatitis (NASH) and liver Cirrhosis.[60] It is critical to treat NAFLD and NASH before it progresses into a more dangerous stage of liver fibrosis. NAFLD and NASH are potentially reversible with lifestyle intervention and potentially by few drugs, but hepatic cirrhosis is an irreversible condition and frequently leads to hepatic-cell failure, hepato-cellular carcinoma and death.[61] Liraglutide has been shown to slow progression of fatty liver disease in a study examining patients with T2D and NASH.[62] A recent multicenter, double-blind, randomized, placebo-controlled phase-two study in patients with NASH (the LEAN study) receiving liraglutide or placebo for about 10 months, 39% of those patients who took liraglutide showed NASH resolution by liver biopsy in comparison to 9% in the placebo group. This finding provides some early evidence that GLP-1 RAs may be clinically effective in treating patients with NASH.

Furthermore, there is evidence that GLP-1 RAs can be used for obesity management. In December 2014, liraglutide became the first FDA approved GLP-1 RA to be indicated for weight-management in conjunction with lifestyle intervention.[63] Semaglutide, while successfully promoting weight-loss, has not been FDA approved for obesity indication yet. Throughout the PIONEER clinical drug trials, patients taking oral semaglutide experienced significant weight loss (dosage-dependent range, −2.1 kg to −6.9 kg) and significant for oral semaglutide dosages of 10 mg or more compared with placebo (−5.7 kg; $P < .001$).[29] There are no current trials specifically focus on treating obesity by oral semaglutide, however it may be expected in the very near future.

Authors' Note

This literature review was conducted using PubMed and Google scholars of meta-analyses and systematic reviews published within the past 10 years, by use of the terms "GLP-1 analog, semaglutide, oral GLP-1, T2D."

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