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REVIEW

A Peptide in a Pill – Oral Semaglutide in the Management of Type 2 Diabetes

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Abstract: T2DM (type 2 diabetes mellitus) is a chronic and progressive illness with high morbidity and death rates. Oral semaglutide (Rybelsus®) is a combination of semaglutide, a glucagon-like peptide-1 receptor agonist (GLP-1 RA), and sodium N- (8- [2-hydroxybenzoyl] amino) caprylate (SNAC), an absorption enhancer that facilitates semaglutide absorption across the gastric epithelium in a concentration-dependent manner. This family of drugs apart from glucose lowering effects causes significant weight loss with lower risk of hypoglycemia, and some of them have been linked to a significant reduced major adverse cardiovascular events. GLP-1 RAs may assist persons with T2DM and chronic kidney disease (CKD), a major microvascular consequence of T2DM, in ways other than lowering blood sugar. Several large clinical studies, the bulk of which are cardiovascular outcome trials, show that GLP-1 RA treatment is safe and tolerated for persons with T2DM and impaired renal function and that it may potentially have renoprotective characteristics. This article focuses on the advances of oral GLP1-RA and describes the key milestones and predicted advantages.

Keywords: type 2 diabetes mellitus, incretin system, GLP-1 receptor agonist, oral semaglutide, pioneer trials

Introduction

Diabetes is one of the most common worldwide public health issues, presenting a significant global burden on public health and socioeconomic development. Although the incidence of diabetes has begun to reduce in certain countries, the prevalence of diabetes has increased in most other developed and developing countries in recent decades.[1] The International Diabetes Federation (IDF) has anticipated that, in 2017, 451 million individuals globally would live with diabetes, with a rise to 693 million by 2045 unless effective preventative techniques are adopted.[2] Genetic and environmental variables, such as inheritance, lifestyle changes, age, socioeconomic position, education, urbanization, and stress, have been associated as potential risk factor that predisposes young individuals to more likely to develop diabetes.[3–5] The etiopathogenesis of T2DM was mostly a combination of two primary factors: deficient pancreatic β-cell insulin production and the failure of insulin-sensitive tissue to respond to insulin.[6]

T2DM is progressive in the pathophysiology leading to persistent hyperglycemia and involves several abnormalities. At least eight different pathophysiological anomalies referred to as the Ominous Octet contribute to glucose homeostasis and occur early in T2DM natural history.[7] The UK prospective diabetes (UKPDS) research provides the first high-quality evidence for the definitive reduction in rates of microvascular complications and long-term macro-vascular diseases by improved Glycemic Control.[8,9] The outcomes were superior to conventional treatments in intensively treated patients, the weight gains and increased risk of hypoglycemias were of particular concern. Readers should be reminded that throughout UKPDS, the use of metformin, sulfonylureas, and insulin, for the most part, was restricted to hypoglycaemic treatments. Improved treatment modalities are the need of the hour for the management of patients with T2DM to attain holistic Diabetes care without or with minimal risk of hypoglycemia GLP-1R as has recently led to a significant breakthrough in our knowledge, the metabolic roles performed by intestine "incretin" hormones help to understand the pathophysiological basis for treating people with type 2 diabetes using incretin-based medicines.[10] As a class, GLP-1

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receptor agonists are becoming increasingly popular among diabetics due to their potent glucose-lowering effects, low risk of hypoglycemia, and potential weight-loss effects. Furthermore, agents within the GLP-1 receptor agonist class have also demonstrated therapeutic benefits for the cardiovascular system and the renal system.[11] Review article based on findings from the Peptide Innovation for Early Diabetes Treatment (PIONEER) program looks at the therapeutic role of GLP-1 RA Oral semaglutide in treating T2D.

Glucose Homeostatic Incretin Systems

The human GLP-1R gene is located on the long arm of chromosome 6p21.[12] The GLP-1R is a 64 kDa protein.[13] Although alternate splicing produces two transcripts for the rat and human GLP-1R,[14,15] only one functionally distinct GLP-1R has been identified so far. There have been numerous polymorphisms associated with the human gene GLP-1R,[12] however linkage analysis indicates that the majority of T2DM cases are not linked with the individual polymorphism.[16–19]

Activating GLP-1Rs can have several positive effects on acute insulin secretion and maintenance of correct β cell glucose sensing, transcriptional synthesis, proliferation, and survival. When GLP-1 agonists engage the receptor, multiple pathways are activated and integrated. Therefore, using GLP-1R agonists for treating chronic β cell failure in T2DM seems to be the most appropriate treatment method. As a key mediator of GLP-1 agonist action, cyclic adenosine monophosphate (cAMP) is present in the acute molecular events leading to insulin secretion when the GLP-1 receptor is expressed in a clonal β cell line. The GLP-1R overexpressing clonal β cell line exhibits a marked increase in resting cAMP levels.[20] cAMP serves as a secondary messenger, especially for many receptors, but its ability to respond specifically to external stimuli and affect signalling pathways is modulated by its formation, degradation, and spatial regulation by anchoring proteins.[21]

GLP-1 is secreted in enteroendocrine cells located in the distal small intestine and colon; plasma level of GLP-1 increases rapidly within minutes of meal intake even before digested nutrients enter the colon, indicating GLP1 secretion at distal L cell is promoted by neural and or endocrine stimuli. Proglucagon is transported by a processing mechanism that needs prohormone convertase-1 to glicentin, oxyntomodulin, GLP-1, and GLP-2 in intestinal L cells. The GLP-1 is produced from GLP-1 (1–37) and is complemented by GLP-1 (7-37) and GLP-1 (7–36) amide as two electric potential molecular circular forms. The majority of the circulating active GLP-1 in human plasma is GLP-1 (7–36) amide.[22] Glucose is considerably more insulin-secretory intake when orally than intravenously delivered (IV). The "incretin effect" phenomenon has been estimated to account for 70% of total insulin production in healthy people in response to oral glucose or a meal.[23,24]

Gut peptides – Glucagon like peptide-1 (GLP-1) and Gastric inhibitor polypeptide (GIP) are nutrient-dependent peptides that stimulate glucose-dependent insulin secretion, promote β-cell proliferation, and inhibit apoptosis. GLP-1, but not GIP, controls glycemia via additional actions on glucose sensors, inhibition of gastric emptying, food intake, and glucagon secretion. The specific process for the selection of incretin hormones by food components is still unclear. The mechanisms in the selective secretion of uncontrolled hormones were revealed to mediate components of the glucose transport system, such as the sodium-glucose transport system 1 (SGLT-1) and the G protein-linked with a long chain of fatty acid receptors of the L cells.[23,25] Finally, during a fasting state, incretin levels of hormones are very low and released by ingestion of glucose and fats. The trigger that begins the enteroinsulinary axis with the release of insulin from pancreatic β-cells is food consumption. Although neural pathways influence the production of insulin, neuronal pathways have no function in the enteroinsulinary axis since GLP-1 does not improve at the cephalic stage of insulin secretion.[26]

In patients with T2DM, GIP with GLP-1 was found to be responsible for more than 80% of the incretin effect that follows after eating any meal. However, this effect could be diminished, and the receptors desensitized over time. Researchers suggested that this was caused by free fatty acids and chronic hyperglycemia. Subsequently, wide-ranging research has been advanced to expand GLP-1 action for a more extended period and hence normalization of plasma glucose in T2DM patients. This resulted in the development of GLP-1 RA and DPP-4 enzyme inhibitors.[27–30] Glucagon-like peptide-1 (GLP-1) is an insulin-stimulating peptide hormone that suppresses glucagon-dependent production. GLP-1

also decreases stomach emptying and lowers appetite, measures that can enhance glycemic management. Several GLP-1RA were created as therapeutic drugs for the treatment of T2DM, which are responsible for GLP-1 inactivation.[31,32]

Anchoring the Incretin Defect with GLP-1RAS

Enhancing the role of incretin-mimetics to augment the GIP responsiveness in poorly controlled Patients with T2DM has been demonstrated to elevate and sustain GLP-mediated effects. DPP4 inhibition strategically increases the half-life of endogenous GLP and GIP in an endogenous incretin-dependent manner, whereas GLP1-RA is resistant to DPP4 enzymatic degradations. DPP4 Inhibitors exercise their effect by stimulating the GLP-1 receptors at physiological levels; in contrast, GLP-1RAs exert their action at Supra physiological levels and help in greater sustainment of activation. With the advent of GLP-1RA, there has been a paradigm shift in the management of type T2D, with effective glucose and weight lowering abilities coupled with cardio renal protective properties.

GLP 1 Agonist

The GLP-1RAs are classified according to their basic structure and pharmacokinetic characteristics. They resist the breakdown by the Dipeptidyl peptidase −4 (DPP4) enzyme by changing the amino acid in the peptide chain. The structure of a natural protein, obtained from the Gila monster saliva, exendin-4 (Ex-4) with considerable similarity to native GLP-1, was synthetically evolved into another group. This natural protein exhibits the receptor-activating characteristics of GLP-1 and is resistant to DPP4 enzyme degradation. They can also be classed according to their duration, apart from structural categorization (short-acting and long-acting GLP-1 RAs).[33] Exenatide (administrated twice daily), liraglutide and lixisenatide (given once every day), and once weekly exenatide-extended-release, albiglutide and dulaglutide are now authorized in the United States for treating type 2 diabetes. Weekly-once dulaglutide is now available in India and has undoubtedly made a significant impact on GLP1-RA's role in managing type 2 DM, despite being injectable as its once-a-week preparation.

A recent update to the Cardiovascular Disease Prevention Guide (CVD) of the American Heart Association/American Diabetes Association (AHA/ADA) highlights a key component of weight management and suggests that the healthcare providers are considering the use of anti-hyperglycemic medicines that cause weight loss, including GLP-1 receptor agonists.[34] The recent guidelines ADA/EASD/AACE recommend the utility of GLP1 RAs higher up in the treatment algorithm in the patients with ASCVD risk and T2DM. GLP-1RA is associated with significant glucose-lowering weight lowering and cardiovascular benefits as described by cardio vascular outcome trials (CVOTs) –LEADER, REWIND, and SUSTAIN 6.

LEADER Study

Liraglutide and cardiovascular outcomes in T2D were the subject of a 2016 study.[35] Participants had T2D and were 50 years old above with at least one co-existing established cardiovascular condition or 60 years plus with at least one cardiovascular risk factor. This trial also used a two-week run-in period of injecting a placebo to increase compliance, and after that, patients were randomly assigned to either 1.8 mg liraglutide (or maximum tolerated dose) or a volume-matched placebo injection. The primary outcome was the incidence of the first composite cardiovascular outcome of death from cardiovascular causes, non-fatal myocardial infarction, or non-fatal stroke.

Participants received an average follow-up of 3.5 years, with 96.8% dying or completing the final visit as a primary outcome. The average baseline HbA1C was 8.7%for all participants, 81.3% had chronic kidney disease and 24.7% had cardiovascular disease. Patients on liraglutide received it 84% of the time during the trial; 13% of participants in liraglutide received the primary composite outcome, significantly lower than 14.9% of participants in the placebo group. The death rate from cardiovascular cause (4.7%, compared to 6.0%, in the placebo group, $p = 0.007$) and the death rate from any cause (8.2%, compared to 9.6% in the liraglutide group, $p = 0.02$) were also significant secondary outcomes.

Lixisenatide: ELIXA

The first CVOT among the GLP-1 RAs was the evaluation of lixisenatide in acute coronary syndrome (ELIXA) trial, published in 2016[36] Participants included were those with T2D who also had an acute coronary event within 180 days

before screening. To increase compliance, they used a run-in period of self-administered placebo injections. Then, the subjects were randomly assigned to receive either lixisenatide or a volume-matched placebo. The patients who were randomly assigned, 6068 of them, were monitored for a median of 25 months. There were 406 patients (13.4%) in the lixisenatide group and 399 patients (13.2%) in the placebo group who experienced a primary end-point event (hazard ratio, 1.02; 95% confidence interval [CI], 0.89 to 1.17). This result demonstrated that lixisenatide was non-inferior to placebo (P0.001) but was not superior (P = 0.81). Both the rate of death (hazard ratio, 0.94; 95% CI, 0.78 to 1.13 in the lixisenatide group) and the rate of hospitalization for heart failure did not differ significantly between the groups.

Once-Weekly Exenatide: EXSCEL

Effects of Once-Weekly Exenatide on Cardiovascular Outcomes in Type 2 Diabetes (EXSCEL), which was completed and published in 2017,[37] was the subsequent CVOT. The HgA1c range for participants with T2D was 6.5% to 10.0%, and the trial was intended to have 70% of participants with prior cardiovascular events. There were 14,752 patients in total who were randomly assigned, and the average follow-up time was 3.2 years. The median baseline HgA1c was 8%, and 73.1% of these participants had cardiovascular disease in the past. 76% of participants received the intended exenatide treatment for the average amount of time. 11.4% of patients in the exenatide group experienced the primary composite outcome, compared to 12.2% of patients in the placebo group, which did not reach significance for superiority.

Albiglutide: Harmony Outcomes

"Albiglutide and cardiovascular outcomes in patients with type 2 diabetes and cardiovascular disease (Harmony Outcomes)" was published in 2018.[38] With T2D and one of the following conditions: established cardiovascular disease, established cerebrovascular disease, or established peripheral arterial disease, 21 participants were 40 years of age or older. There were 9463 total participants, with a median baseline HgA1c of 8.7% and a median study duration of 1.6 years. All participants had a history of coronary artery disease in 71% of cases, peripheral arterial disease in 25%, cerebrovascular disease in 25%, and heart failure in 20% of cases. In the albiglutide group, 24% of participants abruptly stopped taking the medication. Significantly fewer patients in the albiglutide group (7% vs 9% in the placebo group) experienced the primary composite cardiovascular endpoint. With an HR of 0.75 (95% CI 0.61 to 0.90, P = 0.003), the albiglutide group also experienced statistically significant decreases in fatal or non-fatal myocardial infarctions.

AMPLITUDE - O

In this randomised, placebo-controlled trial, which was carried out at 344 sites in 28 countries, we assessed the effectiveness of efpeglenatide in people with type 2 diabetes who also had at least one other cardiovascular risk factor, as well as either a history of cardiovascular disease or current kidney disease. There were 4076 participants in total; 2717 received the medication efpeglenatide, while 1359 received a placebo. Of the 189 participants (7.0%) who were given efpeglenatide (3.9 events per 100 person-years) and 125 participants (9.2%) who were given a placebo (5.3 events per 100 person-years), incident MACEs occurred during a median follow-up of 1.81 years (hazard ratio, 0.73; 95% confidence interval [CI], 0.58 to 0.92; P=0.001 for noninferiority; P = 0.007 for superiority). Of the 353 participants (13.0%) assigned to receive efpeglenatide and 250 participants (18.4%) assigned to receive a placebo, respectively, a composite renal outcome event (a decrease in kidney function or macroalbuminuria) occurred (hazard ratio, 0.68; 95% CI, 0.57 to 0.79; P=0.001).[39]

REWIND

Dulaglutide was the next CVOT, published in 2019.[40] Unlike prior studies, which were aimed at demonstrating non-inferiority, this one was designed to demonstrate superiority. Participants had to be at least 50 years old, had T2D, and had past cardiovascular events or risk factors. A three-week run-in period was included in the trial to promote compliance. After that, participants have given either dulaglutide 1.5 mg or a volume-matched placebo. The primary outcome was the first nonfatal myocardial infarction, nonfatal stroke, or death from cardiovascular or unknown causes.

The study involved a total of 9901 individuals, with an average baseline HgA1c of 7.2% and a median follow-up of 5.4 years. 31.5% of the individuals had a history of cardiovascular disease. From randomization until either the primary endpoint event or final follow-up, participants in the dulaglutide group took the study medicine 82.2% of the time. The

primary cardiovascular composite outcome occurred in 12% of dulaglutide individuals versus 13.4% in the placebo group, which was statistically significant (P = 0.026). Non-fatal stroke was also considerably lower in the dulaglutide group compared to placebo (2.7% vs 3.5%, P = 0.017) in the secondary analysis. Dulaglutide was found to have significantly fewer renal outcomes than the control group (17.1% versus 19.6%, P = 0.0004).

Semaglutide

Semaglutide is an analog to human GLP-1, which has a structural homology of 94% with native human GLP-1 and three significant changes that increase its half-life to around one week in humans. Semaglutide treatment resulted in considerable weight reduction, reduced energy intake, lower hunger, and food gravure, and a reduced relative preference for rich meal energy.[41,42] Semaglutide subcutaneous formulation has been successful in SUSTAIN studies; Semaglutide scores of 0.5 mg and 1 mg decreased from baseline levels of HbA1c by 1.8% and HbA1c levels by less than 7%, with 0.5 mg and 67% to 79% decreased by 1 mg for instances of HbA1c. In Sustain 6, subcutaneous Semaglutide at 0.5 and 1.0 mg decreased HbA1c from baseline by 1.8% and achieved target A1c of less than 7% by 67% and 79% with 0.5mg and 1.0 mg, respectively. The weight of the body has also decreased by up to 6.5 kg. The SUSTAIN 6 study also showed that the main CV events with Semaglutide were reduced significantly compared to placebo in high-risk T2D patients. In individuals treated with Semaglutide vs placebo ($p < 0.001$ for non-inferiority) the hazard ratio (HR) for major adverse cardiac events (MACE) was 0.74 (95% CI 0.58, 0.95).[43–45]

To understand the long-term advantages and safety of the therapies within this class, further GLP-1 RAs safety assessment, particularly assessing pancreatitis, cardiovascular safety, and neoplasms will be essential.[46,47] Subcutaneous Semaglutide proved to have higher CV benefits associated with potential glucose-lowering, weight reducing properties; the only challenge it possessed was mild adverse effects and an injectable route of administration.

SUSTAIN 6 evaluated cardiovascular and other long-term outcomes with Semaglutide in subjects with T2DM.83% of the Cohort had established cardiovascular disease including stage 3 chronic renal disease, 59% had no established CVD but with an average HbA1C- 8.7%. Primary composite endpoints (deaths from cardiovascular events, non-fatal myocardial infarctions, or non-fatal stroke events) occurred in 6.6% of patients on Semaglutide as compared to 8.9% on placebo. The risk of cardiovascular deaths or non-fatal myocardial infarctions did not statistically change in the Semaglutide group; however, there were significant reductions in non-fatal stroke. (1.6%) 2.7% as compared to placebo.[45]

Oral Semaglutide

Semaglutide has been created as an oral formulation to expand therapy choices for patients. Since peptides have poor bioavailability, oral semaglutide is co-formulated into a tablet containing a sodium caprylate (8-[2-hydroxybenzoyl] amino), an absorption enhancing agent that helps prevent proteolytic degradation of semaglutide and supports absorption throughout the stomach mucosa. Recently, numerous RCTs have examined whether oral semaglutide is effective in lowering blood glucose and body weight in T2DM individuals.[48–50] The Pioneer clinical program includes 8 clinical trials that compare semaglutide to placebo, SGLT2 inhibitors, another GLP1-RA, a DPP-4 inhibitor, or as a supplement to insulin. overview of the pioneer program is detailed in Table 1.

Pioneer 1 is a randomized, double-blind placebo-controlled trial in adults with T2DM who had insufficient control with diet and physical activity. They were randomized to Oral Semaglutide 3mg, 7mg, 14mg, and placebo. The primary endpoint was a change in Hba1c at 26 weeks, confirmed by secondary changes in Weight at 26 weeks. Oral Semaglutide as monotherapy demonstrated superior Hba1c reduction across all doses, and weight loss was significant with 14mg vs placebo at the end of the trial. The safety profile of the oral semaglutide was in line with any other established GLP-1 therapy.[51]

Pioneer 2 compared the efficacy and safety of Oral Semaglutide in patients with Uncontrolled T2DM on metformin vs Empagliflozin (SGLT2 inhibitor). This randomized open-label trial with either Empagliflozin or Oral semaglutide over 52 weeks. The study concluded showing Oral Semaglutide was superior to empagliflozin in terms of HbA1c reduction but not weight at 26 weeks, wherein by the end of 52 weeks, both HbA1c and weight reductions were clinically significant with similar tolerability as that of an established GLP-1 receptor agonist.[52]

Pioneer 3 is a randomized, double-blind, double-dummy Phase 3a trial assessing the effect of Hba1c with the addition of oral semaglutide on patients with uncontrolled T2DM on metformin or with Sulphonylurea. Pioneer 3 demonstrated

Table 1 Overview of PIONEER Trails Program

Trails	Cohort (Duration of the Study)	Primary Endpoint	Treatment	HbA1C Change From Baseline	Weight Change (Kgs)	Conclusion
PIONEER 1 (26 weeks)[45]	703 adults with T2D uncontrolled with diet and exercise.	Change in HbA1C from baseline to week 26	Oral Sema 3mg	−0.7	−0.2	Oral semaglutide as monotherapy produced superior and clinically significant reductions in HbA1C with all doses and superior body weight loss with 14mg versus placebo
			Oral Sema 7mg	−1.2	−1	
			Oral Sema 14mg	−1.4	−2.6	
			Placebo	−0.1	-	
PIONEER 2 (52 weeks)[48]	822 adults with T2D uncontrolled on metformin	Change in HbA1C from baseline to week 26	Oral Sema 14mg	−1.4	−3.8	At 26 weeks Oral semaglutide demonstrated superior HbA1C reduction as compared to Empagliflozin, but not body weight. at 52 weeks, oral semaglutide reduced both HbA1C and weight significantly as compared to Empagliflozin
			Empa 25mg	−0.9	-	
PIONEER 3 (72 weeks)[49]	1864 adults with T2D uncontrolled with metformin and/or sulfonylurea	Change in HbA1C from baseline to week 26	Oral Sema 3mg	−0.6	−1.2	The 7 and 14mg/day semaglutide dosages were superior to sitagliptin in reducing HbA1C from baselines at week 26. Non-inferiority of the 3mg/day semaglutide dosage vs sitagliptin could not be demonstrated
			Oral Sema 7mg	−1	−2.2	
			Oral Sema 14mg	−1.3	−3.1	
			Sita 100mg	−0.8	−0.6	
PIONEER 4 (52 weeks)[50]	711 adults with T2D on metformin with or without an SGLT2 inhibitor	Change in HbA1C from baseline to week 26	Oral Sema	−1.2	−4.4	Oral semaglutide proved to be not inferior vs liragultide and Superior to Placebo in decreasing HbA1C and Superior in Body weight reduction vs liragultide and placebo at the end of 26 weeks.
			Lira 1.8	−1.1	−3.1	
			Placebo	−0.2	−0.5	
PIONEER 5 (26 weeks)[51]	324 adults with T2D and moderate renal impairment on metformin and/or sulfonylurea, or basal insulin	Change in HbA1C from baseline to week 26	Oral Sema 14	−1.1	−3.7	Oral semaglutide has been effective in patients with T2D type 2 diabetes and moderate renal impairment, potentially providing a new treatment option for this population
			Placebo	−0.1	−1.1	

PIONEER 6[52]	Event driven study to Assess cardiovascular outcomes in 3183 adult T2D patients of age > 50 years with established cardiovascular disease or CKD, or Age > 60 with cardiovascular risks factors alone.	Time to first occurrence of MACE	Oral Sema 14	3.8% (61/1591)	-	Oral semaglutide was non inferior to placebo
			Placebo	4.8% (76/1592)	-	
PIONEER 7 (52 weeks)[53]	504 adults with T2D inadequately controlled on one of two oral glucose- lowering drugs	Proportion of patients achieving HbA1C less than 7% at week 5	Oral Sema Flex	52.6	−2.4	Higher percentage (63%) of patients achieved HbA1C less than 7 as compared to 28% with Sitagliptin group
			Oral Sema 100mg	28.6	−0.9	
PIONEER 8 (52 weeks)[54]	731 adults with T2D under insulin therapy with or without metformin	Change in HbA1C from baseline to week 26	Oral Sema 3mg	−0.6	−0.9	Oral semaglutide was superior to placebo in reducing HbA1C and body weight when added to insulin with or without metformin in patients with T2D.
			Oral Sema 7mg	−0.9	−2	
			Oral Sema 14mg	−1.3	−3.3	
			Placebo	−0.1	−0.4	
PIONEER 9 (52 weeks)[55]	243 Japanese adults uncontrolled T2D managed by diet or exercise or with oral glucose - lowering drug monotherapy	Change in HbA1C from baseline to week 26	Oral Sema 3mg	−1.1	-	Oral semaglutide provides significant reduction in HbA1C compared with placebo in a dose - dependent manner
			Oral Sema 7mg	−1.5	-	
			Oral Sema 14mg	−1.7	-	
			Lira 0.9	−1.4	-	
PIONEER 10 (52 weeks)[56]	458 uncontrolled T2DM Japanese adults	Number of adverse events over 57 weeks	Oral Sema 3mg	77%	0.0	Oral semaglutide was well tolerated, significantly reduced HbA1C (14mg) and body weight (7, 14) versus weekly subcutaneous Dulaglutide 0.75mg by week 52
			Oral Sema 7mg	80%	−0.9	
			Oral Sema 14mg	85%	−1.6	
			Dulaglutide 0.75mg	82%	−1.0	

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that Oral Semaglutide at 7mg and 14mg had significantly higher HbA1c reductions at the end of 26 weeks; however, 3mg did not show significant benefits.[53]

Pioneer 4 compared the efficacy and tolerability of Oral Semaglutide and Subcutaneous Liraglutide. It is a double-blind double-dummy phase 3a trial, which revealed non-inferiority in decreasing HbA1c and significant superiority in weight reductions at the end of 26 weeks. Safety and tolerability were similar to that of Subcutaneous Liraglutide. Reduced Utilization of GLP-1 receptor agonist as of date was predominantly due to the injectable route of administration, but now with the advent of oral semaglutide, it would potentiate earlier initiation and continuum of diabetes care.[54]

Pioneer 5 evaluated the efficacy and safety of oral semaglutide in patients with T2DM and moderate renal impairment. It is a double-blind phase 3 trial where patients with T2DM and eGFR 30–59 mL/min per 1·73 m2, and who had been receiving a stable dose of metformin or sulfonylurea, or both, or basal insulin with or without metformin for the past 90 days were enrolled efficacy in terms of change in HbA1c and Weight at 26 weeks were analyzed. Oral semaglutide proved to be effective in patients with moderate renal impairment, adding on as a newer treatment option for this population. The safety profile was consistent with any other GLP1 receptor agonist therapy.[55]

Pioneer 6 is an event-driven double-blind study that attempted to examine if oral semaglutide posed an increased cardiovascular risk. An encouraging completion rate (99.7%), a high percentage of patients who continued to receive oral semaglutide (>80%), and full vital status known at the trial conclusion for all randomly assigned patients all imply high validity for the study's conduct and outcomes. Pioneer 6 concluded showing non-inferiority of oral semaglutide to placebo (hazard ratio, 0.79; 95% CI, 0.57 to 1.11), excluding an 80% excess cardiovascular risk.[56]

Pioneer 7 evaluated the long-term efficacy and safety of oral semaglutide and the effect of switch-over from Sitagliptin over 52 weeks. Pioneer 7 demonstrated superior glycemic control and weight reduction. Long-term treatment with flexible-dose adjustment maintained HbA1c with additional weight loss benefits. Switch-over therapy resulted in more number of patients achieving HbA1c targets with lesser glucose-lowering medications, which offers an additional reduction in body weight.[57]

Pioneer 8 evaluated the efficacy, safety, and tolerability of Oral Semaglutide as an add-on therapy to insulin with or without metformin. The study showed that insulin usage is also linked to an increased risk of hypoglycemia. Despite the improved glycemic control achieved with oral semaglutide, the rates of patients with at least one severe or blood glucose-confirmed symptomatic hypoglycemia episode were comparable across treatment groups. When added to insulin in the setting of poorly managed type 2 diabetes, oral semaglutide was superior to placebo in improving glycemic control and reducing body weight over 26 weeks, with significant improvements also found at 52 weeks and with no increase in the risk of hypoglycemia.[58]

Both the Pioneer 9 and 10 study was conducted in the Japanese population; Pioneer 9 study found that Oral semaglutide reduces HbA1c in Japanese patients with T2DM in a dose-dependent manner when compared to placebo and has a safety profile similar to that of a GLP1 Receptor agonist. Pioneer 10 study compared the safety and efficacy of oral semaglutide versus dulaglutide in Japanese T2DM patients. In Japanese individuals with T2DM, oral semaglutide was well tolerated. By week 52, once-daily Oral semaglutide (14 mg dose) significantly reduced HbA1c and body weight (7 mg and 14 mg doses) compared to weekly subcutaneous dulaglutide 0.75 mg.[59,60]

The real effect on cardiovascular outcomes cannot be identified until the end of the SOUL trial, depending on the decision of the FDA about the pooled data for the semaglutide formulations. The SOUL study is a major randomized, double-blind, phase 3 experiment to assess the cardiovascular effects of oral semaglutide in patients with ASCVD or CKD particularly.[45] With preliminary data from LEADER and REWIND studies indicating encouraging renal results, in particular reduction in albuminuria, the function of the GLP-1 RA class in diabetic kidney disease continues to change. The REWIND study partially attributed the reductions in albuminuria to changes in blood pressure. The significant reduction of blood pressure, combined with improvements in albuminuria, is consistent with the LEADER and REWIND results, while the purpose of PIONEER 5 was to assess the safety in CKD patients and its short duration.[45,61,62] Although PIONEER 5 and other GLP-1 RA tests provide early evidence, additional rigorous studies are required to assess CKD results to confirm that oral semaglutide has a favorable renal impact and to further understand the function of GLP-1 RAs in CKD.[55]

The function of semaglutide in secondary prevention is more complicated and cannot be completely clarified until the CVOTs and/or SOUL tests are combined. Because SGLT-2 inhibitors and GLP-1 RAs are currently recommended in the ADA

for patients with cardiac disease or ASCVD, no modifications to personalized therapy prescription based on patient comorbidity would be expected. Even if the efficacy of oral semaglutide is somewhat lower than that of subcutaneous semaglutide, some doctors may choose the GLP-1 RA based on practicality alone.[40] With the novel oral semaglutide formulation, doctors can use GLP-1 RA at early course of diabetes with ASCVD risk and continue with established cardiovascular disease to the stages of requirement for insulin. PIONEER research is a confirmatory evidence that demonstrate that oral semaglutide in comparison to other popular oral antidiabetic substances is capable of producing better metabolism with cardio renal protection and holistic care.

Real-World Evidence

Retrospective analysis of early use of oral semaglutide in routine clinical practice in the IGNITE study from International Business Machine (IBM) explore Electronic Health Record (HER) database revealed 66% of patients were prescribed by primary care physicians, with 54.5% being women with a mean age of 57.8 years. The mean HbA1c change from the baseline was 0.9% and greater A1C reductions were seen in people with a higher baseline. IGNITE indicates earlier adoption of oral semaglutide by primary care physicians and improved real-world glycemic control as seen in pioneer studies.[63,64] Pioneer Real is an ongoing Japanese study to evaluate the effectiveness and side effects of once a day oral semaglutide. The most common adverse effects among all the pioneer trials, nausea was the commonest side effect which was very similar to any of the other established injectable GLP-1RA as on date, proving its good tolerability. Cost of the therapy and mode of administration of the drug are the major drawback seen. Continued evaluations of real-world data would provide greater insights into the translations, uptake, and impact of such innovations in routine diabetes care.[65]

Conclusion

When choosing from the many treatment options available for T2DM patients, including the numerous incretin-based therapies, there are various factors to consider. Oral Semaglutide has been demonstrated to be efficacious, safe, and well tolerated for people with T2DM and concomitant overweight/obese, as well as atherosclerotic cardiovascular disease, the medicine should become first-line therapy. Apart from its utility in management of Obese T2D, FDA has recently approved injectable Semaglutide for chronic weight management in adults with obesity or overweight. Recent evidences recommend utility of Semaglutide for non-alcoholic steatohepatitis (NASH) as resolution was achieved with no worsening of fibrosis. It should also be beneficial for people who are at a higher risk of hypoglycemia and prefer oral treatment to injection delivery. More clinical trials and experience will help us better comprehend the drug's advantages.

Furthermore, the availability of oral semaglutide may be a viable option for patients who prefer not to use injectable therapy as it would offer Cardio Renal benefits as evidenced by the various GLP-1RA-based trials. The goal of administering the oral formulation is to improve patient adherence, which is critical for reducing complications and co-morbidities and controlling blood glucose levels. It could be argued that comparing oral semaglutide or injectable semaglutide to other medications not included in the Pioneer program, which differ in terms of methodologies, dosage, and treatment time, is a study limitation. The outcomes of the PIONEER program will need to be validated in real-world situations in the future to ensure that they apply to clinical practice.

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