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REVIEW

Oral Semaglutide, A New Option in the Management of Type 2 Diabetes Mellitus: A Narrative Review

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ABSTRACT

According to current guidelines, glucagon-like peptide-1 (GLP-1) receptor agonists are the antidiabetic agent of choice in patients with type 2 diabetes mellitus (T2DM) and established cardiovascular disease (CVD) and are also the preferable antidiabetic agent in patients with T2DM without CVD but with indicators of high cardiovascular risk. A limitation in the use of GLP-1 receptor agonists is that they are delivered by subcutaneous injections. In this context, the development of an orally administered formulation of semaglutide offers an additional option in the management of patients with T2DM. In the present review, we discuss the findings of the main trials that evaluated the safety and efficacy of oral semaglutide. Oral semaglutide appears to be more effective in reducing HbA_{1c} levels and body weight than other antidiabetic agents and similarly effective to other GLP-1 receptor agonists. The safety profile of oral semaglutide is also comparable with other members of its class. Even though oral semaglutide did not reduce the incidence of the composite primary endpoint in a randomized controlled trial, a reduction in cardiovascular and all-cause mortality was observed. Therefore, oral semaglutide appears to represent a useful tool in the management of patients with TD2M, particularly those with established CVD or high cardiovascular risk and unwilling to receive injectable GLP-1 receptor agonists.

Keywords: Cardiovascular disease; Glucagon-like peptide-1 receptor agonists; Oral semaglutide; Type 2 diabetes mellitus; Weight

Key Summary Points

Oral semaglutide reduces HbA_{1c} and body weight more than other oral antidiabetic agents

Oral semaglutide induces comparable reductions in HbA_{1c} and body weight with injectable glucagon-like peptide-1 receptor agonists

The safety profile of oral semaglutide is also similar with injectable glucagon-like peptide-1 receptor agonists

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INTRODUCTION

According to current guidelines, glucagon-like peptide-1 (GLP-1) receptor agonists are the antidiabetic agent of choice in patients with type 2 diabetes mellitus (T2DM) and established cardiovascular disease (CVD) [1]. Moreover, GLP-1 receptor agonists are also the preferable antidiabetic agent in patients with T2DM without CVD but with indicators of high cardiovascular risk, including age $\geq$ 55 years, coronary, carotid or lower extremity artery stenosis > 50%, left ventricular hypertrophy, estimated glomerular filtration rate (GFR) < 60 ml/min/1.73m^2 or albuminuria [1]. Notably, these agents should be considered independently of the baseline HbA_{1c} levels and HbA_{1c} target [1]. Large randomized controlled trials showed that once-daily liraglutide as well as once-weekly semaglutide and dulaglutide reduce cardiovascular morbidity in patients with T2DM and increased cardiovascular risk [2–4].

A limitation in the use of GLP-1 receptor agonists is that they are delivered by subcutaneous injections. In this context, the development of an orally administered formulation of semaglutide offers an additional option in the management of patients with T2DM. In the present review, we discuss the findings of the main trials that evaluated the safety and efficacy of oral semaglutide as well as the effects of this agent on cardiovascular outcomes and its cost-effectiveness.

METHODS

The PubMed database was reviewed for papers published up to June 2020 using the terms "diabetes," "glucagon-like peptide-1 receptor agonists" and "oral semaglutide." The references of pertinent articles were also hand-searched for relevant papers. Only studies published in English were considered. This article is based on previously conducted studies and does not contain any studies with human participants or animals performed by any of the authors.

PHARMACOLOGY OF ORAL SEMAGLUTIDE

Oral semaglutide is coformulated with the absorption enhancer sodium *N*-[8-(2-hydroxybenzoyl) aminocaprylate] (SNAC) [5, 6]. SNAC has been shown to be safe [6–8]. It has been proposed that SNAC increases pH around the tablet, thus protecting semaglutide from degradation by pepsin and by the acidic gastric pH [5]. Moreover, SNAC appears to promote the formation of semaglutide monomers, which are more easily absorbed [5]. Furthermore, SNAC enhances the absorption of semaglutide by inducing membrane fluidization and surface epithelial sloughing in the gastric mucosa [5]. Coadministration of semaglutide with lisinopril, digoxin and warfarin in healthy subjects did not affect the area under the plasma concentration-time curve and the maximum plasma concentration of the latter medications [9]. On the other hand, the plasma concentration-time curve of metformin increased by 32% when coadminstered with semaglutide, whereas its maximum plasma concentration did not change [9]. However, this increase in exposure to metformin does not appear to be clinically relevant [9]. In another study, coadministration of omeprazole did not affect the plasma concentration-time curve and maximum plasma concentration of semaglutide [10]. Food intake reduces the absorption of semaglutide, and therefore patients must wait 30 min before eating after taking semaglutide [8]. Impairment of hepatic or renal function does not appear to affect the pharmacokinetics of semaglutide [11, 12].

The Peptide InnOvatioN for Early DiabEtes Treatment (PIONEER) program compared the safety and efficacy of semaglutide with placebo as well as with other oral and injectable antidiabetic agents (Table 1).

Oral Semaglutide Compared with Placebo

In the PIONEER-1 trial, 703 patients with T2DM managed by diet and exercise alone were randomized to receive once-daily oral semaglutide 3, 7 or 14 mg or placebo for 26 weeks [13].

Table 1 Major studies that evaluated the safety and efficacy of oral semaglutide

Study	Ref	*n*	Follow-up (weeks)	Baseline treatment	Comparator drug	Dosage of semaglutide	Major findings
PIONEER-1	13	703	26	Diet and exercise alone		3, 7 or 14 mg/day	Semaglutide reduced HbA_{1c} and weight by 0.7–1.4% and 0.2–2.6 kg more than placebo, respectively Treatment discontinuation: 2.3–7.4% and 2.2%, respectively
PIONEER-8	18	731	52	Insulin with or without metformin		3, 7 or 14 mg/day	Semaglutide reduced HbA_{1c} and weight by 0.5–1.2% and 0.9–3.3 kg more than placebo, respectively Nausea: 1.6–3.3 times more frequent in the semaglutide arm
PIONEER-7	14	504	52	1–2 oral antidiabetic agents	Sitagliptin 100 mg/day	3, 7 or 14 mg/day	More patients achieved HbA_{1c} levels $< 7\%$ in the semaglutide group (63 vs. 28% in the sitagliptin group) and mean weight loss was 2.2 kg greater in the former
PIONEER-3	16	1864	78	Metformin with or without sulfonylurea	Sitagliptin 100 mg/day	3, 7 or 14 mg/day	Semaglutide 7 and 14 mg/day reduced HbA_{1c} and weight more than sitagliptin (by 0.3 and 0.7%, respectively, and by 1.6 and 2.4 kg, respectively) Treatment discontinuation rates: 15.0, 19.1 and 13.1%, respectively
PIONEER-2	17	822	52	Metformin	Empagliflozin 25 mg/day	14 mg/day	Semaglutide reduced HbA_{1c} and body weight by 0.4% and 0.9 kg more than empaglifozin, respectively Gastrointestinal adverse events were more common with semaglutide

Table 1 continued

Study	Ref	*n*	Follow-up (weeks)	Baseline treatment	Comparator drug	Dosage of semaglutide	Major findings
PIONEER-4	15	711	52	Metformin with or without a SGLT-2 inhibitor	Liraglutide (dose escalated to 1.8 mg/day)	Up to 14 mg/day	Semaglutide reduced HbA_{1c} by 0.2 and 1.2% more than liraglutide and placebo, respectively, and body weight by 1.5 and 4.0 kg more than liraglutide and placebo, respectively Rates of adverse events were similar in the semaglutide and liraglutide group and lower in the placebo group
PIONEER-5[a]	19	324	26	Metformin or sulfonylurea, or both, or basal insulin with or without metformin		Up to 14 mg/day	Semaglutide reduced HbA_{1c} and weight by 1.1% and 3.7 kg more than placebo, respectively Treatment discontinuation due to adverse events: 15 and 5%, respectively
PIONEER-9[b]	20	243	52		Liraglutide 0.75 mg/day	14 mg/day	Semaglutide and liraglutide induced similar reductions in HbA_{1c} (1.7 and 1.4%, respectively) Constipation, which was the most frequent adverse event, occurred in 13 and 19% of patients, respectively

Table 1 continued

Study	Ref	*n*	Follow-up (weeks)	Baseline treatment	Comparator drug	Dosage of semaglutide	Major findings
PIONEER-10[b]	21	458	52		Once-weekly dulaglutide 0.75 mg	14 mg/day	Semaglutide 14 mg/day induced greater reductions in HbA_{1c} (1.7 vs. 1.4%, respectively) and in weight (− 1.6 vs. 1.0 kg, respectively) Rates of adverse events leading to treatment discontinuation: 6 and 3%, respectively

PIONEER Peptide InnOvatioN for Early DiabEtes Treatment, *T2DM* type 2 diabetes mellitus, *SGLT* sodium-glucose co-transporter

[a] Patients had moderate renal impairment (estimated glomerular filtration rate 30–59 ml/min/1.73 m^2

[b] Study performed in Japanese patients

Semaglutide induced dose-dependent reductions in HbA_{1c} (by 0.7, 1.2 and 1.4% more than placebo, respectively) and in body weight (by 0.2, 1.0 and 2.6 kg more than placebo, respectively) [13]. Nausea and diarrhea were the most common adverse events in patients treated with semaglutide and resulted in treatment discontinuation in 2.3, 4.0 and 7.4% of patients, respectively, compared with 2.2% in patients treated with placebo [13].

In the PIONEER-8 study, 731 patients with T2DM uncontrolled on insulin with or without metformin were randomized to receive oral semaglutide 3, 7 or 14 mg/day or placebo for 52 weeks [14]. Semaglutide yielded dose-dependent reductions in HbA_{1c} (0.5, 0.9 and 1.2% more than placebo) and in body weight (0.9, 2.0 and 3.3 kg more than placebo) [14]. However, the incidence of nausea was also dose-dependently higher in patients treated with semaglutide (1.6–3.3 times higher) [14].

Oral Semaglutide Compared with Other Oral Antidiabetic Agents

In the PIONEER-7 study, 504 patients with T2DM uncontrolled on 1–2 oral antidiabetic agents were randomized to receive oral semaglutide with flexible dose adjustments to 3, 7 or 14 mg/day or sitagliptin 100 mg/day for 52 weeks [15]. The proportion of patients who achieved HbA_{1c} levels < 7% was greater in the semaglutide group (63 vs. 28% in the sitagliptin group), and mean weight loss was 2.2 kg greater in the former [15].

In the PIONEER-3 study, 1864 patients with T2DM uncontrolled with metformin with or without sulfonylurea were randomized to receive once-daily oral semaglutide 3, 7 or 14 mg or sitagliptin 100 mg/day for 78 weeks [16]. Semaglutide induced dose-dependent reductions in HbA_{1c} and at the dose of 7 and 14 mg/day was more effective in reducing HbA_{1c} than sitagliptin (difference, 0.3 and 0.7%, respectively) [16]. Semaglutide also induced dose-dependent reductions in body

weight that were greater than those of sitagliptin at 78 weeks in all semaglutide doses (difference, 0.8, 1.6 and 2.4 kg with the 3, 7 or 14 mg/day dose, respectively) [16]. Treatment discontinuation rates in the semaglutide 3, 7 or 14 mg and sitagliptin groups were 16.7, 15.0, 19.1 and 13.1%, respectively [16].

In the PIONEER-2 study, 822 patients with T2DM uncontrolled on metformin were randomized to receive oral semaglutide 14 mg/day or empagliflozin 25 mg/day for 52 weeks [17]. Semaglutide reduced HbA_{1c} and body weight more than empaglifozin (mean treatment difference 0.4% and 0.9 kg, respectively) [17]. On the other hand, gastrointestinal adverse events were more common with oral semaglutide [17].

Oral Semaglutide Compared with Injectable Antidiabetic Agents

In the PIONEER-4 study, 711 patients with T2DM uncontrolled despite treatment with metformin (≥ 1500 mg/day or maximum tolerated dose) with or without a sodium-glucose cotransporter-2 inhibitor were randomized to receive once-daily oral semaglutide (dose escalated to 14 mg), once-daily subcutaneous liraglutide (dose escalated to 1.8 mg) or placebo for 52 weeks [18]. Semaglutide reduced HbA_{1c} by 0.2 and 1.2% more than liraglutide and placebo, respectively, and also reduced body weight by 1.5 and 4.0 kg more than liraglutide and placebo, respectively [18]. Rates of adverse events were similar in the semaglutide and liraglutide group and lower in the placebo group [18].

Oral Semaglutide in Special Populations

Studies in special populations yielded similar results. In PIONEER-5, 324 patients with T2DM and moderate renal impairment (estimated GFR 30–59 ml/min/1.73 m^2) who were receiving metformin or sulfonylurea, or both, or basal insulin with or without metformin, were randomly assigned to receive oral semaglutide (dose escalated to 14 mg once daily) or placebo for 26 weeks [19]. Oral semaglutide reduced HbA_{1c} by 1.1% and body weight by 3.7 kg more than placebo [19]. However, treatment discontinuation due to adverse events was three times higher with oral semaglutide (15% vs. 5% in the placebo group) [19].

In PIONEER-9, a 52-week, randomized trial in 243 Japanese patients with T2DM, oral semaglutide 14 mg/day induced similar reductions in HbA_{1c} with once-daily liraglutide 0.75 mg (1.7 vs. 1.4 percentage points, respectively) [20]. On the other hand, the incidence of constipation, which was the most frequent adverse event, was lower in the semaglutide group (13 vs. 19% in the liraglutide group) [20].

In PIONEER-10, a 52-week randomized trial in 458 Japanese patients with T2DM, oral semaglutide 14 mg/day induced greater reductions in HbA_{1c} than once-weekly dulaglutide 0.75 mg (1.7 vs. 1.4 percentage points, respectively) and in body weight (− 1.6 vs. 1.0 kg, respectively) [21]. However, the rate of adverse events leading to discontinuation of treatment was two times higher in the semaglutide group (6 vs. 3% in the dulaglutide group) [21].

Meta-Analyses of the Safety and Efficacy of Oral Semaglutide

In a network meta-analysis of 27 randomized controlled studies, oral semaglutide 14 mg/day induced greater reductions in HbA_{1c} than once-weekly dulaglutide 0.75 mg, twice-daily exenatide, once-weekly exenatide 2 mg, liraglutide 1.2 mg and lixisenatide [22]. In addition, oral semaglutide yielded similar reductions in HbA_{1c} with once-weekly semaglutide, once-weekly dulaglutide 1.5 mg and liraglutide 1.8 mg [22]. Moreover, oral semaglutide 14 mg/day induced similar weight loss with once-weekly semaglutide and greater than all other GLP-1 receptor agonists [22]. Oral semaglutide 14 mg/day also induced similar reductions in systolic and diastolic blood pressure with all other GLP-1 receptor agonists except once-weekly semaglutide 1.0 mg, which induced greater reductions in systolic blood pressure (SBP) [22]. The incidence of gastrointestinal adverse events did not differ between the various GLP-1 receptor agonists [22].

EFFECTS OF ORAL SEMAGLUTIDE ON CARDIOVASCULAR MORBIDITY AND MORTALITY

The effects of oral semaglutide on cardiovascular events was evaluated in the PIONEER-6 trial, a randomized placebo-controlled trial in 3183 patients with T2DM who were ≥ 50 years old and had established CVD or chronic kidney disease or were ≥ 60 years with cardiovascular risk factors only [23]. The trial was designed to rule out an 80% excess cardiovascular risk compared with placebo [noninferiority margin of 1.8 for the upper boundary of the 95% confidence interval (CI) for the hazard ratio (HR) for the primary outcome] [23]. After a median follow-up of 15.9 months, the incidence of the primary outcome (the first occurrence of a major adverse cardiovascular event, i.e., death from cardiovascular causes, nonfatal myocardial infarction or nonfatal stroke) did not differ between the groups assigned to receive semaglutide or placebo (3.8 vs. 4.8%, respectively; HR 0.79, 95% CI 0.57–1.11, $p < 0.001$ for noninferiority) [23]. Notably, rates of death from cardiovascular causes were lower in patients treated with oral semaglutide (0.9 vs. 1.9% in the placebo group, HR 0.49, 95% CI 0.27–0.92), and rates of death from any cause were also lower in the former (1.4 vs. 2.8% in the placebo group, HR 0.51, 95% CI 0.31–0.84) [23]. Semaglutide reduced HbA_{1c} by 0.7% more than placebo and body weight by 3.4 kg more than placebo [23]. In addition, the reductions in systolic blood pressure (SBP), low-density lipoprotein cholesterol and triglyceride levels were greater in the former [23]. On the other hand, rates of treatment discontinuation were higher in the semaglutide group (11.6 vs. 6.5% in the placebo group), primarily because of nausea, vomiting and diarrhea [23]. In PIONEER-6, when patients with established CVD or established heart failure were analyzed separately, there was no effect of semaglutide on the incidence of major adverse cardiovascular events, i.e., cardiovascular death and nonfatal myocardial infarction or stroke [24]. Similarly, semaglutide had no effect on cardiovascular morbidity in patients without established CVD or heart failure [24]. Interestingly, in a recent network meta-analysis of seven trials in 56,004 patients, oral semaglutide reduced cardiovascular mortality more than exenatide, dulaglutide and lixisenatide and was similarly effective with liraglutide and once-weekly injectable semaglutide [25].

COST-EFFECTIVENESS OF ORAL SEMAGLUTIDE

In a recent cost-effectiveness analysis, oral semaglutide 14 mg/day was associated with lower cost for achieving HbA_{1c} levels < 6.5% or < 7.0% than dulaglutide, exenatide (once weekly and twice daily), liraglutide and lixisenatide, whereas once-weekly semaglutide 1.0 mg had comparable cost [26]. In a similar study, oral semaglutide 14 mg/day was associated with lower cost for achieving HbA_{1c} levels < 6.5% or < 7.0%, for achieving ≥ 1.0%-point HbA_{1c} reduction and weight loss ≥ 3.0% and for achieving HbA_{1c} levels < 7.0% without hypoglycemia and without weight gain than empagliflozin, sitagliptin and liraglutide [27]. In another recent cost-effectiveness analysis, oral semaglutide 14 mg/day was more cost-effective than empagliflozin and sitagliptin and was also both more effective and less expensive than liraglutide [28].

ORAL VERSUS INJECTABLE SEMAGLUTIDE

Even though there are no studies that directly compared oral and injectable semaglutide, a network meta-analysis suggested that these two formulations of semaglutide have comparable safety and induce similar reductions in HbA_{1c} and body weight [22]. However, once-weekly injectable semaglutide induces greater reductions in SBP than oral semaglutide [22]. Moreover, in the Trial to Evaluate Cardiovascular and Other Long-term Outcomes with Semaglutide in Subjects with Type 2 Diabetes (SUSTAIN-6), once-weekly semaglutide reduced the incidence of the primary endpoint (the first occurrence of cardiovascular death, nonfatal myocardial

infarction, or nonfatal stroke) by 26% compared with placebo in a population with similar size (n = 3297) and characteristics as the PIONEER-6 trial [3]. However, the follow-up period of SUSTAIN-6 was longer than in PIONEER-6 (24 vs. 15.9 months, respectively), and this might have contributed to the different results of the two studies [3, 23]. In addition, once-weekly semaglutide did not reduce cardiovascular or all-cause mortality in contrast to oral semaglutide, which reduced the incidence of both these outcomes [3, 23]. In a network meta-analysis, oral and once-weekly injectable semaglutide yielded similar reductions in cardiovascular mortality [25]. Cost-effectiveness of these two formulations also appears to be comparable [26]. Given the similar safety, efficacy and cost-effectiveness of oral and injectable semaglutide, the choice between the two formulations should be based on patients' preferences (oral vs. once weekly administration).

CONCLUSIONS

Oral semaglutide appears to be more effective in reducing HbA_{1c} levels and body weight than other antidiabetic agents and similarly effective as other GLP-1 receptor agonists. The safety profile of oral semaglutide is also comparable to other members of its class. Even though oral semaglutide did not reduce the incidence of the composite primary endpoint in the PIONEER-6 trial, a reduction in cardiovascular and all-cause mortality was observed. Therefore, oral semaglutide appears to represent a useful tool in the management of patients with TD2M, particularly those with established CVD or high cardiovascular risk and unwilling to receive injectable GLP-1 receptor agonists. Future studies should further evaluate the effects of oral semaglutide on both cardiovascular events and the microvascular complications of T2DM. In addition, studies in specific subgroups, including those with and without established cardiovascular disease as well as in those with diabetic nephropathy, will add new insights into the role of this agent in the management of T2DM.

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