MINI-REVIEW

Semaglutide: The First Oral Glucagon-like Peptide 1 Agonist

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ABSTRACT

Objective: The objective of the study was to review the efficacy and safety of the first orally available glucagon-like peptide (GLP-1) receptor agonist semaglutide. **Methods:** PubMed search published in English, French, and Spanish from January 2000 to December 2, 2019. Search terms included "oral semaglutide," "semaglutide," GLP-1 receptors, "clinical trials," "absorption," "metabolism," "efficacy," "safety," "cardiovascular (CV)," and "kidney disease." **Results:** Oral semaglutide is effectively absorbed in the stomach by absorption enhancer but has to be taken in the fasting state with water, and no food is allowed for 30 min after intake. It is generally comparable in efficacy to the subcutaneous form of semaglutide. Oral semaglutide is slightly superior in decreasing hemoglobin A1c and weight compared with liraglutide, sitagliptin, and empagliflozin. Limited data suggest that oral semaglutide may be used in patients with moderate degree of renal impairment. A large randomized trial of median follow-up of 15.9 months showed that oral semaglutide was non-inferior to placebo in terms of CV events and mortality. In all head-to-head trials, rates of premature drug discontinuation due to adverse effects were greater with oral semaglutide compared with comparator, predominantly due to gastrointestinal adverse effects. **Conclusions:** Oral semaglutide has an efficacy and safety profile consistent with the class of GLP-1 receptor agonists. It represents a useful therapeutic option for patients with type 2 diabetes who are reluctant to take injections.

Key words: Absorption enhancer, efficacy, glucagon-like peptide receptor agonist, oral semaglutide, renal impairment, safety

INTRODUCTION

Oral semaglutide is the only orally available glucagon-like peptide (GLP-1) receptor agonist approved by the Federal Drug Administration in September 2019 under the name of Rybelsus.[1] To achieve adequate bioavailability after oral administration, coformulation with an absorption enhancer is needed. Thus, oral semaglutide is being developed as a coformulation with the absorption enhancer sodium N-[8-(2-hydroxybenzoyl)amino]caprylate.[2] The mode of action of the latter enhancer involves a localized increase in pH that protects semaglutide against proteolytic degradation and facilitates its absorption across the gastric epithelium.[2] Oral semaglutide should be taken in the fasting state because food may hinder its absorption from the stomach.[2] After intake, time to maximum plasma concentration ranges between 0.38 h and 0.7 h.[3] Plasma half-life of oral semaglutide is approximately 1 week, which is similar to semaglutide administered subcutaneously.[3]

EFFICACY OF ORAL SEMAGLUTIDE

Comparison with subcutaneous weekly semaglutide

The efficacy of oral semaglutide is dose dependent and seems inferior to the subcutaneous formulation of semaglutide when used in doses lower than 20 mg/d. Thus, in one Phase 2 randomized trial, reduction in levels of hemoglobin A1c (HbA1c) with oral semaglutide at daily doses of 10 mg was 1.2% versus placebo, whereas the corresponding decrease

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with subcutaneous semaglutide (1.0 mg weekly) was 1.6%.[4] Meanwhile, the efficacy of the 20-mg dose of oral semaglutide was not statistically different from the subcutaneous form (−1.4% and −1.6% vs. placebo, respectively).[4] Unfortunately, in the latter study, the currently recommended 14-mg dose of oral semaglutide was not used.[4]

Comparison with other GLP-1 agonists

In a randomized, double-blind, and double dummy trial, oral semaglutide was compared to the widely used GLP-1 receptor agonist liraglutide (given subcutaneously once daily) and placebo.[5] After 52 weeks, HbA1c reduction in the semaglutide group was 0.3% greater than liraglutide and 1.0% greater than in placebo group.[4] From a mean baseline HbA1c levels of 8.0%, proportions of patients who reached HbA1c <7.0% were 60.7% and 55% in the oral semaglutide and liraglutide group, respectively ($P = 0.11$).[5]

Comparison with sitagliptin

Oral semaglutide was shown to be more effective than sitagliptin 100 mg/d in another randomized, double-blind, and double dummy trial including patients with type 2 diabetes uncontrolled on metformin ± sulfonylurea (SU).[6] After 26 weeks, HbA1c reduction from baseline was −1.0%, −1.3%, and −0.8% with oral semaglutide 7 mg/d, 14 mg/d, and sitagliptin 100 mg/d, respectively.[6]

Comparison with empagliflozin as add-on to metformin

This trial is of important clinical relevance because both GLP-1 agonists and sodium-glucose cotransporter 2 (SGLT2) inhibitors, represented here by empagliflozin, are recommended as second-line therapy when diabetes is not controlled by metformin alone.

Thus, Rodbard *et al*.[7] compared oral semaglutide 14 mg/d with empagliflozin 25 mg/d in patients with type 2 diabetes poorly controlled on metformin with baseline HbA1c levels of 8.1%.[7] Oral semaglutide provided greater HbA1c reduction at 26 weeks (primary outcome) compared with empagliflozin, 1.3% and 0.9%, respectively ($P < 0.0001$).[7] This significant difference in HbA1c levels persisted at 52 weeks.[7] In addition, weight loss was more pronounced with oral semaglutide (4.7 kg) versus empagliflozin (3.8 kg) at 52 weeks ($P = 0.01$).[7] Meanwhile, empagliflozin was better tolerated than oral semaglutide. Thus, adverse effects resulting in premature drug discontinuation occurred in 4.4% and 10.7% of patients, respectively.[7] Most (8% of 10.7%) of withdrawals in the oral semaglutide group were due to gastrointestinal (GI) side effects.[7] The main limitation of this trial, which is funded by the semaglutide manufacturer, is its open-label design. Therefore, it may open to multiple bias.[7] It should be emphasized that recent cardiovascular (CV) outcome studies showed significant and robust decrease in heart failure hospitalization with three SGLT2 inhibitors.[8-10] Moreover, CV and all-cause death were decreased with empagliflozin and dapagliflozin in patients with established CV disease and heart failure, respectively.[8,11] Therefore, in patients with type 2 diabetes and CV disease or heart failure, the author prefers to use one of these two SGLT2 inhibitors rather than oral semaglutide as second-line therapy after metformin.

Oral semaglutide added to insulin

Oral semaglutide was compared in a double-blind design to placebo as add-on therapy to ongoing insulin in patients with type 2 diabetes with baseline HbA1c of 8.2%.[12] Baseline average daily insulin dose was 58 units. Insulin doses were reduced by 20% from randomization to week 8 to avoid hypoglycemia but can be freely adjustable during weeks 26–52.[12] HbA1c reduction at 26 weeks (primary outcome) with oral semaglutide (14 mg/d) and placebo was 1.3% and 0.1%, respectively.[12] Compared to baseline, mean daily insulin doses at 52 weeks decreased by 7 units in the semaglutide group (14 mg/d) and increased by 10 units in the placebo group. At 52 weeks, body weight decreased by 3.7 kg with oral semaglutide and increased by 0.5 kg with placebo.[12] Incidence of severe hypoglycemia (blood glucose <56 mg/dl) did not differ between semaglutide and placebo.[12] Premature discontinuation of the study drug was higher with oral semaglutide (13.3%) compared with placebo (2.7%), mainly due to GI adverse effects (10.5% vs. 0.5%).[12] Thus, the above results suggest that the addition of oral semaglutide to ongoing insulin therapy significantly decreases HbA1c levels, body weight, and insulin requirements without increasing hypoglycemia. These advantages are at the expense at increase in GI adverse effects.

EFFECT OF ORAL SEMAGLUTIDE ON BODY WEIGHT

Similar to other members of GLP-1 receptor agonists, oral semaglutide consistently induces weight loss close to 4 kg compared to placebo after 52 weeks.[5] In the largest randomized trial of oral semaglutide, mean reduction in weight at 62 weeks compared with baseline was 4.2 kg in the oral semaglutide group and 0.8 kg in the placebo group (statistical significance was not reported).[13] Inspection of weight curves showed that maximum weight reduction was attained between 26 and 38 weeks followed by mild rebound.[13]

USE OF ORAL SEMAGLUTIDE IN CHRONIC KIDNEY DISEASE

The pharmacokinetics of oral semaglutide was not affected in subjects with renal impairment.[14] In fact, semaglutide is metabolized by proteolytic cleavage and not cleared by specific organ.[14] In one randomized, double-blind, and placebo-controlled trial of 26 weeks duration, oral

semaglutide was effective in patients with advanced type 2 diabetes and Stage 3 chronic kidney disease (CKD) defined as estimated glomerular filtration rate (eGFR) between 30 and 59 ml/min/1.73 m^2.[15] The reduction in HbA1c value was 1.0% compared to baseline and 0.8% compared with placebo.[14] In addition, mean reduction in weight was 3.4 kg and 0.9 kg in the oral semaglutide and placebo, respectively, with a significant difference of 2.5 kg.[15] However, oral semaglutide seems less well tolerated in patients with CKD. Hence, 15% discontinued oral semaglutide due to adverse effects compared with 5% in placebo.[15] Overall, renal function as reflected by eGFR was unchanged throughout the trial in both treatment groups.[15] Clearly, more studies are needed with longer duration of follow-up to establish renal safety of oral semaglutide in patients with various degrees of CKD.

EFFECT OF ORAL SEMAGLUTIDE ON CV OUTCOMES

PIONEER 6 is the largest randomized trial available for the evaluation of CV safety of oral semaglutide.[13] The main purpose of the PIONEER 6 trial is to test whether oral semaglutide is non-inferior to placebo in terms of CV outcomes in patients with type 2diabetes and high CV risk at baseline. An overview of trial design is summarized in Table 1.

After a median follow-up of 15.9 months, the primary outcome composed of CV death, non-fatal myocardial infarction (MI), and non-fatal stroke occurred in 3.8% of patients randomized to oral semaglutide and 4.8% of those randomized to placebo corresponding to 21% risk reduction (hazard ratio 0.79, 95% confidence interval [CI], 0.57–1.11), $P < 0.001$ for non-inferiority, but $P = 0.17$ for superiority.[13]

In addition, oral semaglutide was associated with decreased risk in death from any cause (1.4% vs. 2.4% placebo, hazard ratio 0.51, 95% CI 0.31–0.84) and death from CV causes (0.9% vs. 1.9% placebo, hazard ratio 0.49, 95% CI 0.27–0.92). There was a non-significant trend in risk reduction in the semaglutide group in non-fatal stroke and in heart failure requiring hospitalization, and inverse trend toward increases risk of nonfatal MI and unstable angina requiring hospitalization.[13] Nevertheless, these data provide reassurance about short-term CV safety of oral semaglutide and are in line with the results of CV trials of other members of GLP-1 receptor agonists,[16,17] including subcutaneous semaglutide.[18]

SAFETY OF ORAL SEMAGLUTIDE

In general, the safety profile of oral semaglutide is consistent with the class of GLP-1 receptor agonists. Indeed, GI adverse effects, particularly nausea, are the most common adverse effect reported by 20% of patients receiving oral semaglutide compared with 4% with placebo.[5] Moreover, GI adverse effects were the most common cause of permanent drug discontinuation in 11.6% of patients randomized to oral semaglutide compared to 6.5% of those randomized to placebo.[13]

Table 1: Overview and main results of PIONEER 6[13]

Design	**Randomized, double-blind, multicenter, two groups**
Patients	*n*=3183 with type 2 diabetes, mean age 66 y/o, 31% of females, 85% had established cardiovascular disease, baseline HbA1c 8.2%
Main outcome	Time to first occurrence of cardiovascular death, non-fatal myocardial infarction, or non-fatal stroke
Median follow-up	15.9 months
Concomitant diabetes medications at baseline	Metformin 77%, insulin 60%, sulfonylureas 32%, sodium-glucose cotransporter -2 inhibitors 10%
Intervention	Oral semaglutide 14 mg/d (*n*=1591), placebo (*n*=1592)
Number of events of primary outcome	Semaglutide 61 (3.8%), placebo 76 (4.8%), HR* 0.79 (95% confidence interval [CI] 0.57–1.11)
Death from any cause	Semaglutide 23 (1.4%), placebo 45 (2.8%), HR 0.51 (95% CI 0.31–0.84)
Mean change in weight compared with baseline	Semaglutide −4.2 kg, placebo −0.8 kg
Mean change in HbA1c compared with baseline	Semaglutide −1.0%, placebo −0.3%
Patients with severe hypoglycemia	Semaglutide 23 (1.4%), placebo 13 (0.8%)
Discontinuation of the study drug due to adverse effects	Semaglutide 11.6%, placebo 6.5%

*HR: Hazard ratio. Difference in primary outcome was statistically significant (*P*<0.001) for non-inferiority of oral semaglutide compared to placebo, but non-significant (*P*=0.17) with respect to superiority of semaglutide over placebo. HbA1c: Hemoglobin A1c

In an attempt to predict tolerance of oral semaglutide in clinical practice, one randomized open-label trial used flexible dose of oral semaglutide (n = 253) versus sitagliptin 100 mg/d (n = 250).[19] At week 52, of the 212 patients on semaglutide, 41% could not tolerate the maximum dose (14 mg/d) due to nausea and vomiting and were receiving either the 7-mg dose (30%) or the 3-mg dose (9%).[19]

Severe hypoglycemia requiring assistance of another person occurred in 1.4% and 0.8% of patients receiving oral semaglutide and placebo, respectively. All severe hypoglycemic events occurred in patients taking concomitant insulin or SU.[13]

Worsening of diabetic retinopathy was previously reported in a large trial of subcutaneous semaglutide occurring in 3.0% of subjects compared with 1.8% of patients receiving placebo (hazard ratio, 1.76, 95% CI 1.11–2.78, P = 0.02).[18] In PIONEER 6, the proportions of patients with adverse effects related to retinopathy were numerically greater with oral semaglutide, 7.1% versus 6.3% with placebo.[13] However, patients with baseline diabetic retinopathy were excluded from the study.[13] One long-term trial specifically designed to investigate the relationship between subcutaneous semaglutide and retinopathy is underway and should further clarify this issue.

WHO IS THE BEST CANDIDATE FOR ORAL SEMAGLUTIDE?

Based on the drug characteristics and available data discussed above, oral semaglutide may be appropriate add-on second- or third-line drug for patients with type 2 diabetes uncontrolled on metformin and other oral agents who are overweight and reluctant to take any form of injections. In addition, oral semaglutide may be useful for patients prone to hypoglycemia and those with moderate renal impairment.

Patients with proliferative retinopathy should not use any form of semaglutide until more safety data become available. Advantages and limitations of oral semaglutide are summarized in Table 2.

Table 2: Advantages and limitations of oral semaglutide.[1,5,14]

Advantages

- Taken orally once daily
- Comparable efficacy to subcutaneous semaglutide and liraglutide
- Causes moderate weight loss, approximately 3–4 kg after 1 year
- Low risk of hypoglycemia, except when used with insulin or SU
- May be used in moderate renal impairment (eGFR 30–59 ml/min/1.73 m^2).

Limitations

- Has to be taken on empty stomach with water and not to take any drink or food or other oral medications for at least 30 min after
- Common GI adverse effects (10–15% vs. 2–5% with placebo)
- Takes 8 weeks of dose escalation to reach maximum dose (14 mg/d), leading to delay to reach maximum efficacy
- Its long-term safety not established, particularly its effect on worsening retinopathy.

CONCLUSIONS AND FUTURE NEEDS

No doubt, oral semaglutide provides a practical treatment option for patients with type 2 diabetes. This oral formulation is as effective as the subcutaneous form of semaglutide and slightly more effective than liraglutide, sitagliptin, and empagliflozin. The drug profile of oral semaglutide closely mimics other drugs pertaining to the class of GLP-1 agonists including mild weight loss, decrease risk of hypoglycemia, possible decrease in CV events, but increase in GI adverse effects. Randomized trials of adequate power are needed to establish long-term efficacy and safety of oral semaglutide in a broader population of patients with type 2 diabetes having different degrees of CV risk factors and renal function at baseline. These trials should carefully examine safety issues of particular concern such as worsening of diabetic retinopathy.

CONFLICTS OF INTEREST

The author has no conflicts of interest to declare.

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