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Oral Semaglutide for the Treatment of Type 2 Diabetes: A Mini Review

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Abstract

Objective: *To review efficacy and safety of the first orally available glucagon-like peptide-1 (GLP-1) receptor agonist semaglutide.*

Methods: *PubMed search published in English, French and Spanish from January 2000 until September 04, 2019. Search terms included "oral semaglutide", "semaglutide", "GLP-1 receptors", "clinical trials", "absorption", "metabolism", "efficacy", "safety", "cardiovascular", "kidney disease". Randomized trials, review articles, expert opinions and editorials are included in the review.*

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 allowed for 30 min after intake. It is generally comparable in efficacy to the subcutaneous form of semaglutide. When compared to liraglutide, oral semaglutide is slightly superior in decreasing hemoglobin A1c (HbA1c) (-0.3% vs. liraglutide) and weight (-1.3 kg vs. liraglutide), but is associated with more frequent adverse effects (reported by 80% vs. 74% of patients). Oral semaglutide was more effective than sitagliptin. Limited data suggest that oral semaglutide is safe and effective 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 cardiovascular events and mortality, and might have beneficial effects on reducing some of these events.*

Conclusion: *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. Further studies are needed to establish its long-term efficacy and safety in a large population of type 2 diabetes, including those with chronic kidney disease.*

Keywords: oral semaglutide, absorption enhancer, GLP-1 receptor agonist, efficacy, safety, renal impairment

Abbreviations: GLP-1: glucagon-like peptide-1; HbA1c: hemoglobin A1c; CKD: chronic kidney disease; eGFR: estimated glomerular filtration rate; CV: cardiovascular; GI: gastrointestinal; MI: myocardial infarction

Introduction

Oral semaglutide is the only orally available GLP-1 receptor agonist. To achieve adequate bioavailability after oral administration, co-formulation with an absorption enhancer is needed. Thus, oral semaglutide is being developed as a co-formulation with the absorption enhancer sodium N-[8-(2-hydroxybenzoyl)amino]caprylate (SNAC) [1]. 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 [1]. Oral semaglutide should be taken in the fasting state because food may hinder its absorption from the stomach [1]. After intake, time to maximum plasma concentration ranges between 0.38 h–0.7 h [2]. Plasma half-life of oral semaglutide is approximately 1 week, which is similar to semaglutide administered subcutaneously [2].

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 HbA1c with oral semaglutide at daily doses of 10 mg was 1.2% *vs.* placebo, whereas the corresponding decrease with subcutaneous semaglutide (1.0 mg weekly) was -1.6% [3]. Meanwhile, the efficacy of the 20 mg dose of oral semaglutide was not statistically different from the subcutaneous form of semaglutide (1.4% and -1.6% *vs.* placebo, respectively) [3]. Unfortunately, in the latter study, the currently recommended 14 mg dose of oral semaglutide was not used [3].

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 [4]. 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 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) [4].

Comparison with sitagliptin

Oral semaglutide was shown to be more effective than sitagliptin 100 mg/d in another randomized, double-blind, double-dummy trial including patients with type 2 diabetes uncontrolled on metformin ± sulfonylurea (SU) [5]. 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 [5].

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 [4]. 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) [6]. Inspection of weight curves showed that maximum weight reduction was attained between 26 and 38 weeks followed by rebound [6].

Use of Oral Semaglutide in Chronic Kidney Disease

The pharmacokinetics of oral semaglutide were not affected in subjects with renal impairment [7]. In fact, semaglutide is metabolized by proteolytic cleavage, and not cleared by specific organ [7]. In one randomized, double-blind, placebo-controlled trial of 26-week 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 30–59 ml/min/1.73 m^2 [8]. The reduction in HbA1c value was 1.0% compared to baseline and 0.8% compared with placebo [8]. 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 [8]. 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 [8]. Overall, renal function as reflected by eGFR was unchanged throughout the trial in both treatment groups [8]. Clearly, more studies with longer duration of follow-up are needed to establish renal safety of oral semaglutide in patients with various degrees of CKD.

Effect of Oral Semaglutide on Cardiovascular Outcomes

PIONEER 6 is the largest randomized trial available for the evaluation of cardiovascular (CV) safety of oral semaglutide [6]. 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 2 diabetes and high CV risk at baseline. An overview of trial design is summarized (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% CI, 0.57–1.11), $P < 0.001$ for non-inferiority, but $P = 0.17$ for superiority [6].

Design	**Randomized, double-blind, multi-center, 2 groups**
Patients	n = 3183 with type 2 diabetes, mean age 66 y/o, 31% 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% 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 study drug due to adverse effects	Semaglutide 11.6%, placebo 6.5%

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

In addition, oral semaglutide was associated with decreased risk of 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 increase risk of non-fatal MI and unstable angina requiring hospitalization [6]. Nevertheless, these data provide reassurance about short-term CV safety of oral semaglutide, and are in line with results of CV trials of other members of GLP-1 receptor agonists [9, 10], including subcutaneous semaglutide [11].

Safety of Oral Semaglutide

In general, the safety profile of oral semaglutide is consistent with the class of GLP-1 receptor agonists. Indeed, gastrointestinal (GI) adverse effects, particularly nausea, are the most common adverse effect reported by 20% of patients receiving oral semaglutide compared with 4% with placebo [4]. Moreover, GI adverse effects were the

commonest cause of permanent drug discontinuation in 11.6% of patients randomized to oral semaglutide compared to 6.5% of those randomized to placebo [6].

In an attempt to predict tolerance of oral semaglutide in clinical practice, one randomized open-label trial compared flexible dose of oral semaglutide (n = 253) *vs.* sitagliptin 100 mg/d (n = 250) [12]. 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%) [12]. 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 [6].

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) [11]. In PIONEER 6, the proportions of patients with adverse effects related to retinopathy were numerically greater with oral semaglutide, 7.1% *vs.* 6.3% with placebo [6]. However, patients with baseline diabetic retinopathy were excluded [6]. 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 an 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 for hypoglycemia and those with moderate renal impairment.

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

Advantages	**Limitations**
Taken orally once daily	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
Comparable efficacy to subcutaneous semaglutide and liraglutide	Common GI adverse effects (10–15% *vs.* 2–5% with placebo)
Causes moderate weight loss, approximately 3–4 kg after 1 year	Takes 8 weeks of dose escalation to reach maximum dose (14 mg/d) leading to delay to reach maximum efficacy
Low risk of hypoglycemia, except when used with insulin or SU	Its long-term safety not established, particularly its effect on worsening retinopathy
May be used in moderate renal impairment (eGFR 30–59 ml/min/1.73 m^2)	

Table 2: Advantages and limitations of oral semaglutide.

Conclusion 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 at least as effective as liraglutide. 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 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 conflict of interest to declare.

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