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Mini review

Once weekly semaglutide for treatment of obesity

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Abstract

Background: Once weekly (OW) semaglutide 0.5-1.0 mg is a glucagon-like type-1 receptor agonist (GLR-1 RA) approved for treatment of type 2 diabetes and is currently under evaluation for treatment of obesity at a higher dose of 2.4 mg OW.

Objective: to provide an appraisal of OW semaglutide 2.4 mg for treatment of obesity.

Methods: Pubmed research up to March 22. Randomized trials, pertinent animal studies, and reviews are included. Search terms were glucagon-like type 1 receptor agonists, weight loss, obesity, semaglutide, safety, efficacy.

Results: OW semaglutide 2.4 mg was evaluated as a weight loss agent in 3 well-designed clinical trials of 68 week-duration. In one trial including patients with type 2 diabetes, the difference in weight loss from baseline to week 68 between OW semaglutide and placebo was - 6.2 percentage points (95% CI, -7.3 to -5.2; P<0.0001). In the other 2 studies that excluded patients with diabetes, the difference in weight loss between OW semaglutide and placebo ranged between -10.3% and -12.4%. A significantly higher proportion of participants in the semaglutide groups vs placebo groups achieved at least 5% of weight loss. The most common adverse effects of semaglutide were related to the gastrointestinal (GI) system. Across these 3 trials, premature discontinuation of OW semaglutide occurred in 6-7% vs 3% in placebo groups.

Conclusions: OW semaglutide may be a promising agent for treatment of obesity irrespective of presence of type 2 diabetes. Further studies are needed to establish its long-term safety and efficacy.

Key words: obesity; semaglutide; glucagon-like polypeptide 1; safety, weight loss

Introduction

GLP-1 RAs are approved for treatment of type 2 diabetes. The drug profile of these drugs is characterized by mild dose-related weight loss of approximately 2-6 kg [1]. Currently, liraglutide is the only GLP-1 RA approved for treatment of obesity in a dose higher than that approved for type 2 diabetes (3 mg daily for treatment of obesity as opposed to maximum dose of 1.8 mg/d in type 2 diabetes) [2]. Semaglutide is a long-acting GLP-1 RA that can be administered once weekly in a dose of 0.5-1.0 mg for treatment of type 2 diabetes [3]. Since the magnitude of weight loss increases with the dose of GLP-1 RA, semaglutide is being evaluated as weight-loss agent at a higher weekly dose of 2.4 mg [4-7]. The Semaglutide Treatment Effect in People with obesity (STEP) development program includes 5 phase 3 clinical trials (STEP 1 to 5) to evaluate efficacy and safety of OW semaglutide at this high dose of 2.4 mg for treatment of obesity in patients with and without diabetes [4]. Three trials of the STEP program have been published [5-7]. The purpose of this article is to provide an appraisal of OW semaglutide for treatment of obesity, with special emphasis on its efficacy and safety in this setting.

Rationale for evaluation of semaglutide as treatment of obesity

Data from trials of patients with type 2 diabetes suggest that OW 1.0 mg semaglutide is superior to other GLP-1 RAs such OW exenatide ER 2 mg, OW dulaglutide 1.5 mg, and daily liraglutide 1.2 mg in terms of reduction of weight and hemogolobin A1c (HbA1c) levels [1,8,9]. In addition, a meta-analysis of indirect comparison between semaglutide and the sodium-glucose transporter 2 inhibitor empagliflozin has shown that OW 1.0 mg semaglutide was more effective than empagliflozin 25 mg/d in reducing weight (estimated treatment difference -1.65 kg, 95% CI, -2.22 to -1.08, P<0.0001) [10]. Furthermore, OW 1.0 mg semaglutide has been shown to decrease cardiovascular (CV) events in patients with type 2 diabetes who were at high cardiovascular risk [11]. Therefore, the STEP program was launched to evaluate the weight-loss effects of OW

semaglutide 2.4 mg. This program consists of 5 trials, three of them were published [4-7].

Mechanisms of weight loss by semaglutide

In a randomized, double-blind trial including 72 obese subjects (mean weight 105.5kg), OW semaglutide was associated with 35% ad libitum energy intake compared with placebo after 20 weeks [12]. In addition, semaglutide significantly reduced hunger and food craving, and increased satiety and fullness versus placebo [12]. Importantly, gastric emptying, evaluated indirectly via paracetamol absorption, was not delayed in the semaglutide group after controlling for difference in weight between the semaglutide group and placebo group [12]. Animal studies have shown that the anorexigenic of semaglutide is mediated by GLP-1 receptors in the hypothalamus and hind brain [13,14].

STEP program

STEP 1 to 3 trials are generally well-designed studies comparing OW 2.4 mg semaglutide with placebo in obese individuals (defined as BMI of $\geq$ 30 kg/m^2, over $\geq$ 27 kg/m^2 with $\geq$ 1 weight-related coexisting condition e.g. hypertension, dyslipidemia, cardiovascular disease, or obstructive sleep apnea) for 68 week-duration [5-7]. Overview of STEP trials was summarized in table 1, Trials STEP 1 and 3 excluded patients with diabetes, whereas STEP 2 included exclusively patients with type 2 diabetes. In addition, STEP 2 included a third group of individuals randomized to the smaller anti-diabetic dose of semaglutide (OW 1.0 mg) [6]. In STEP 1 and 2, all participants receive lifestyle intervention defined as a 500 kcal deficit relative to the estimated energy expenditure plus encouragement of increase physical activity, such as walking 150 minutes per week. In STEP 3 trial, all subjects received a low-calorie diet (1000-1200 kcal/d) provided as meal replacement for the first 8 weeks. Subsequently, they were transitioned to a low-calorie diet (1200-1800 kcal/d) of conventional food. Moreover, they were prescribed 200 min of physical activity/week [7]. The coprimary endpoints of STEP 1 to 3 trials were the percentage change in body weight and weight reduction of at least 5% at week 68 compared with placebo [5-7].

Weight loss in STEP 1-3 trials

Weight loss started in the first few weeks after starting semaglutide and reached a nadir after 52-60 weeks [5-7]. In all STEP trials, semaglutide was significantly superior to placebo in the magnitude of weight loss. Thus, in STEP 1-3, semaglutide-treated subjects lost 6.2 to 10.3 percentage points greater than placebo after 68 weeks [5-7]. In STEP 2 that exclusively included patients with type 2 diabetes, the difference in weight loss vs placebo was relatively small (6.2 percentage point) [6]. The explanation of this finding is unclear but might be related to the coexistence of type 2 diabetes, relatively older patient population (mean age 55 in STEP 2 versus 46 year-old in STEP 1 and 3), or the lower baseline body weight (99.8 kg in STEP 2 versus approximately 105.5 kg in STEP 1 and 3). Across the STEP 1-3 trials, percentage of subjects who achieved $\geq$ 5% weight loss at 68 weeks was significantly greater with semaglutide than with placebo, 69-86% and 28-48%, respectively (Table 1) [5-7]. A subgroup analysis (n=140) in STEP 1 trial using dual-energy x ray absorptiometry (DXA) has shown that semaglutide administration was associated with reduction in total fat and regional visceral fat mass and to a lesser extent reduction in lean body mass [5].

Glycemic effects of OW semaglutide in STEP trials

In STEP 2 trial, mean HbA1c reductions were -1.6%, -1.5%, and -0.4% in the OW semaglutide 2.4 mg, OW semaglutide 1.0 mg, and placebo groups, respectively [6]. HbA1c levels were also reduced by approximately 0.2 to 0.3 percentage points in patients without diabetes in STEP 1 and 3 trials [5, 7]. Moreover, in STEP 1, 84.1 % of participants who had prediabetes at baseline reverted to normoglycemia at 68 weeks. Corresponding proportion was 47.8% in the placebo group [5].

Effects of OW semaglutide on cardiovascular risk factors in STEP trials

Significant reduction in systolic blood pressure (SBP) was recorded in subjects randomized to semaglutide in STEP1-3 trials, approximately 4-5 mmHg lower than in individuals randomized to placebo [5-7]. Likewise, a significant reduction in DBP of approximately 2 mmHg was observed in STEP 1 and 3 trials [5, 7]. Changes in lipid panel were generally mild. Thus, reduction in plasma triglycerides of 14-17% compared to placebo was the most consistent change in lipid panel. Minor reductions in concentrations of low-density lipoprotein-cholesterol (LDL-C) (by $\leq$7% vs placebo) and increase in high-density lipoprotein-cholesterol (HDL-C) levels (by <5% vs placebo) were also observed. In addition, there was significant reduction in the inflammatory marker C-reactive protein (CRP) levels in semaglutide-treated subjects vs placebo [5-7]. The above favorable changes in blood pressure, lipids and CRP are likely attributed to weight loss per se and are unlikely to be direct effects of semaglutide.

Effects of semaglutide on physical functioning and quality of life

Greater improvements in physical functioning scores and quality of life were seen with semaglutide than with placebo [5, 6].

Safety of once weekly semaglutide 2.4 mg

Overall, OW semaglutide 2.4 mg was fairly tolerated. This conclusion is based on the proportions of subjects who discontinued trial drug prematurely due to adverse effects, 5.9-7% in semaglutide groups versus 2.9-3.5% in the placebo groups across STEP 1 to 3 trials [5-7]. It was somewhat reassuring that over 68 weeks of semaglutide therapy, no signals of increased incidence of cancer or pancreatitis were observed.

Gastrointestinal adverse effects

In STEP 1-3, GI adverse effects were the most common events reported by approximately 63-83% and 34-63% in subjects randomized to OW semaglutide and placebo, respectively [5-7]. Among the GI adverse effects, nausea was the most frequent, followed by diarrhea, vomiting and constipation. The frequency of GI symptoms increased early in the first few weeks during drug titration. They were generally described as mild to moderate and transient. However, they were severe in a minority of patients. In fact GI adverse effects were the most frequent cause of premature drug withdrawal. Thus, drug discontinuation due to GI adverse effects occurred in 3.4-4.5% and 0-1.0% in patients randomized to OW semaglutide and placebo, respectively [5-7].

Previous trials in type 2 diabetes using OW 1.0 mg semaglutide have shown that GI adverse effects tend to be more common with semaglutide compared with other GLP-1 agonits [15]. Meanwhile, post-hoc analysis by Lingway et al [15] suggest that GI adverse effects contribute minimally (less than 0.1 kg) to the superior weight loss effects of semaglutide vs other GLP-1RA agonists. Incidence of cholelithiasis and cholecystitis was slightly higher in STEP 1 and 3 trials (2.5-2.6% with semaglutide versus 0-1.2% with placebo) [5, 7]. These events are attributed in part due to weight loss, but other mechanisms could be involved such as inhibition of gallbladder contraction and biliary motility [16].

Diabetic retinal disorders

Worsening diabetic retinopathy was observed previously in association with use of OW semaglutide 0.5-1.0 mg [11]. In STEP 2, there was a trend towards increase in incidence of retinal disorder events in the 2 semaglutide arms compared with the placebo arm [6]. Thus, these events occurred in 6.9%, 6.2%, and 4.2% in patients randomized to OW semaglutide 2.4 mg, OW semaglutiude 1.0 mg, and placebo, respectively (statistical significance level was not reported). No doubt, this safety issue requires further studies.

Hypoglycemia

In STEP 2 trial, severe or blood-glucose confirmed symptomatic hypoglycemia occurred in 5.7% and 3.0% of patients receiving OW semaglutide 2.4 mg and placebo, respectively [6]. Interestingly, in patients without diabetes, frequency of hypoglycemia with OW semaglutide was low (0.5-0.6%) and similar to placebo (0-0.8%) [5-7].

Advantages and limitations of semaglutide

OW semaglutide 2.4 mg offers several advantages as potential drug for treatment of obesity. First, its short-term efficacy and safety are supported by 3 well-designed randomized trials [5-7]. Second, being an anti-diabetic drug, it may be particularly useful in obesity-related type 2 diabetes by causing reduction of both weight and hyperglycemia [6]. Third, the OW administration of semaglutide may enhance prolonged drug adherence. Meanwhile, OW semaglutide has several limitations. First, the common occurrence of GI adverse effects represents one of the most important limitations of OW semaglutide. Second, the duration of therapy in clinical trials was short (68 weeks) [5-7]. Thus, the durability of its weight loss effect is still unknown. In fact, in the full-analysis set of STEP1-3 trials, the maximum weight loss was achieved after 52 weeks followed by a slight rebound [5-7]. Therefore, it is unclear to what extent weight regain may occur after stopping the drug. Indeed, in the STEP1-3 trials, follow-up extended for 7 weeks after trial end to evaluate short-term safety. Unfortunately, the investigators did not report any weight data at this time period after the end of drug admnistration. Nevertheless, the ongoing STEP 4 will address this issue as it includes a group of subjects who switch from semaglutide to placebo [4]. Third, long-term safety of OW semaglutide for several years is unknown. The ongoing STEP 5 may in part clarify this problem as it extends over a 2-year period [4]. Fourth, drug cost is virtually another limitation. Advantages and limitations of OW semaglutide are summarized in table 1.

Trial	STEP 1 [5]	STEP 2 [6]	STEP 3 [7]
Design	Randomized, double-blind, PL-controlled, 2 groups, 2:1 ratio	Randomized, double blind, double-dummy, PL-controlled, 3 equal groups	Randomized, double-blind, PL-controlled, 2 groups, 2:1 ratio
Patients	N=1961, 74.1% W, mean age 46, mean weight 105 kg, mean BMI 37.9 kg/m^2	N=1210 with type 2 diabetes, 50.9% W, mean age 55, mean weight 99.8 kg, mean BMI 35.7 kg/m^2, mean HbA1c 8.1%	N=611, 81.0% W, mean age 46, mean weight 105.8 kg, mean BMI 38.0 kg/m^2
Intervention	S 2.4 mg OW (n=1306) vs PL (n=655) + lifestyle intervention in all patients	S 2.4 mg OW (n=404), S 1.0 mg OW (n=403), PL (n=403) + lifestyle intervention in all patients	S 2.4 mg WO (n=407) PL (n=204) + intensive behavioral therapy + low-calorie in the first 8 weeks in all patients
Percentage mean weight loss from baseline	S -14.9% vs PL -2.4%, difference -12.4% (95% CI, -13.4 to -11.5%, P <0.001)	S 2.4 mg -9.6% vs PL -3.4%, difference -6.2% (95% CI -7.3 to -5.2, P <0.0001). S 1.0 mg -7.0%	S 2.4 mg -16.0% vs PL -5.7%, difference -10.3% (95% CI, -12.0 to -8.6, P <0.0001)
Percentage of patients with > 5% weight loss	S 86.4% vs PL 31.5%, (P <0.001)	S 2.4 mg 68.8% vs PL 28.5%, OR 4.88 (95% CI, 3.5 to 6.64, P<0.0001). S 1 mg 57.1%	S 2.4 mg 86.6% vs PL 747.6% (P< 0.0001)
Percentage of patients with >10% weight loss	S 69.1% vs PL 12.0% P<0.001	S 2.4 mg 45.6% vs PL 8.2%. P value not mentioned.	S 2.4 mg 75.3% vs PL 27.0% (P<0.001)
Discontinuation of trial drug due to adverse effects	S 2.4 mg 7.0% vs PL 3.1%	S 2.4: 6.2%, S 1.0 5.0%, PL 3.5%	S 2.4 5.9% vs PL 2.9%
Serious adverse effects	S 2.4 9.8% vs PL 6.4%	S 2.4 9.9%, S1 7.7%, PL 9.2%	S 2.4 5.7% vs PL 0%

Table 1: *Overview of STEP trials*

Abbreviations

W: women, BMI: body mass index, S: semaglutide, OW: once weekly, PL: placebo, HbA1c: hemoglobin A1c, CI, confidence intervals

Conclusions and current directions

Overall, once weekly semaglutide 2.4 mg added to healthy life-style changes represents a promising new drug for treatment of obesity given

its acceptable short-term efficacy and safety. Longer term trials are underway to evaluate the durability of its weight loss action and long-term safety. The incidence of cancer and possible worsening of diabetic retinopathy should be carefully examined during the studies underway. In addition, the impact of OW semaglutide on CV events and mortality is unknown, In this regard, the SELECT study is an ongoing, double-blind placebo-controlled trial specifically designed to examine the effect of OW semaglutide 2.4 mg on CV outcomes in overweight and obese persons with established CV disease who do not have diabetes. This SELECT study started in November 2018 and is expected to recruit 17,500 participants, and last for approximately a total of 59 months. Data derived from this large trial should further clarify the safety profile of OW semaglutide.

Conflict of interest

The authors do not have any conflict of interest.

Advantages

Acceptable weight loss efficacy
Amelioration of HbA1c levels in patients with type 2 diabetes
Easy administration once weekly

Limitations

Common occurrence of gastrointestinal adverse effects
Lack of long-term efficacy and safety data
Expected high cost

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