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Review Article

Cagrilintide Combined with Semaglutide: a new Approach for Treatment of Obesity and type 2 Diabetes

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Abstract:

Cagrilintide is a long-acting amylin receptor agonist that lowers body weight and controls hyperglycemia through various actions. In a phase 2 trial of obese subjects, cagrilintide used in different subcutaneous doses once weekly was associated with a mean weight loss of 6-10.8% after 26 weeks, compared with 9.0% with the glucagon-like 1 receptor (GLP-1R) liraglutide (3 mg/d) and 3% with placebo at 26 weeks. In another phase 2 trial of obese patients with type 2 diabetes, the combination of cagrilintide 2.4 mg/week and the GLP-1R semaglutide 2.4 mg/week (referred to as CagriSema) was compared with each drug alone. At 32 weeks, reduction in glycated hemoglobin (HbA1c) levels with CagriSema (2.2%) was statistically superior to Cagrinlitide (0.9%), but not statistically greater than semaglutide (1.8%). Meanwhile, weight loss with CagriSema (15.6%) was statistically greater than both cagrilintide (8.1%) and semaglutide (5.1%). Higher proportions of patients (58%) randomized to CagriSema reported gastrointestinal (GI) adverse effects compared with those who received cagrinlitide (33%) and semaglutide (32%). In addition, level 1 hypoglycemia (blood glucose 55-69 mg/dl) occurred more frequently with CagriSema (7%) and cagrilintide (6%) versus 0% with semaglutide. In conclusion, reduction in obese patients with type 2 diabetes, preliminary data suggest that the combination of cagrilintide and semaglutide may exert a synergistic effect on weight loss but less than additive effect of HbA1c levels. This combination was associated with higher rates of GI adverse effects and mild hypoglycemia. Phase 3 clinical trials are urgently needed to clarify the efficacy and safety of this new approach for treatment of obesity and type 2 diabetes.

Keywords: cagrilintide; semaglutide; cagrisema; obesity; diabetes

Summary

Amylin is a 37 amino acid pancreatic hormone co-secreted with insulin from β-cells following meals [1]. This hormone exerts several actions that result in glycemic control including slowing of gastric emptying and suppression of postprandial glucagon release [1]. In addition, amylin may lower body weight by decreasing appetite and increasing satiety [2]. Pre-clinical data suggests that amylin may affect hedonic aspects in eating control and reduce the rewarding value of food [2]. The latter effects are mediated through receptors in the central nervous system such as the caudal hindbrain area postrema and the hypothalamic arcuate [2]. Moreover, while obesity is characterized by resistance to leptin, amylin may improve body responsiveness to leptin [3]. The first available amylin agonist was pramlintide, which is already approved for treatment of type 1 and type 2 diabetes in conjunction with insulin [4]. Yet, pramlintide has a short half-life (20-45 min) and therefore must be injected subcutaneously 3 times daily before meals. Furthermore, pramlintide causes only modest mean weight loss of 1.6 kg and HbA1c reduction of 0.34% compared with placebo [4]. Cagrilintide is a long-acting acylated agonist of amylin receptor [1]. The half-life of cagrilintide is 159-195 hours (approximately 6.6 to 8.1 days) making it suitable for once weekly subcutaneous administration [5]. Semaglutide is a GLP-1R agonist approved for treatment of type 2 diabetes (in doses 0.5-2.0 mg once weekly) and obesity (2.4 mg once weekly) [6,7]. The anti-diabetic actions of semaglutide include stimulation of insulin secretion, inhibition of glucagon secretion after meals and delay of gastric emptying [8]. Its anti-obesity effects are related to decrease appetite and induction of early satiety [8]. Despite some overlap in actions exists between cagrilintide and semaglutide, the combination of the 2 agonists was investigated to enhance their efficacy. Thus, preliminary data from a phase 1b trial showed that use of cagrilintide and semaglutide in obese subjects resulted in greater weight loss than semaglutide alone, 17% versus 10% after 20 weeks [5]. Subsequently, cagrilintide was evaluated as monotherapy for treatment of obesity in a phase 2 trial and in combination with semaglutide for treatment of obese patients with type 2 diabetes in another phase 2 trial [9,10]. Table 1 depicts the overview of these 2 trials. The main purpose of this article is to review efficacy and safety of cagrilintide with special emphasis on its combination with semaglutide.

Cagrilintide monotherapy for treatment of obesity

In a 26-week phase 2 trial (n=706, 62% women, mean age 52 years), cagrilintide was evaluated in 5 groups of subjects receiving 0.3, 0.6, 1.2, 2.4, and 4.5 mg/week as treatment for obesity in comparison with liraglutide 3.0 mg/day, and placebo (table 1) [9]. The study was conducted in 57 sites from 10 countries. It was double-blinded, randomized, and placebo-controlled [9]. Subjects with diabetes were excluded. Baseline body weight and body mass index (BMI) were 10.7.4 kg and 37.8% kg/m^2, respectively [9]. All participants received dietary and exercise counselling aiming at 500-kcal deficit per day. At 26 weeks, mean percentage reductions in weight (the primary outcome) were 6.0% to 10.8% in the cagrilintide groups compared with 9.0% in the liraglutide group, and 3.0% with placebo [9]. Compared with placebo, weight loss achieved with all doses of cagrilintide was statistically significant, estimated difference range was 3.0% to 7.8% (P<0.001) [9]. In addition, weight reduction with the highest dose of cagrilintide was superior to liraglutide, estimated difference 1.8% (P< 0.03) [9]. The weight loss with cagrilintide was dose-related and progressive without evidence of a plateau up to the end of treatment at 26 weeks [9]. Similarly, the trajectory of liraglutide-induced weight loss did not exhibit any attenuation during the treatment period [9].

Cagrilintide combined with semaglutide (CagriSema) for treatment of type 2 diabetes

In a recent small phase 2 trial (n=92), 3 groups of patients with type 2 diabetes were randomized to receive cagrilintide co-administered with semaglutide (the authors called this combination CagriSema), cagrilintide or semaglutide, both in doses escalated to 2.4 mg once weekly (table 1) [10]. The 2 drugs were injected subcutaneously in the same time in 2 separate sites in the abdomen. Patients were also obese with mean weight of 105.7 kg and BMI of 35.5 kg/m^2 (table 1) [10]. Background diabetes therapy included metformin and sodium-glucose transporter-2 inhibitor (SGLT2i) in 73% and 27% of patients, respectively [10]. At 32 weeks, the mean change in HbA1c levels from baseline (the primary endpoint) was -2.2%, -1.8%, and -0.9% with CagriSema, semaglutide, and cagrilintide, respectively (table 1) [10]. Estimated difference in HbA1c reduction between CagriSema and cagrilintide was statistically significant: -1.3% (95% CI, -1.7 to -0.8; p< 0.0001) [10]. However, corresponding difference between CagriSema and semaglutide was not significant being -0.4% (95% CI, -0.8 to 0.0, p=0.075) [10]. HbA1c values attained a plateau in the 2 groups of patients receiving CagriSema and semaglutide at 20 weeks, whereas in the cagrinlitide group the decrease in HbA1c was more gradual and was progressive up to the end of treatment at 32 weeks [10]. One secondary endpoint in this trial was the comparison of glycemic parameters in the 3 groups by using continuous glucose monitoring (CGM) device worn for 10 days at baseline, week 20 and week 32 [10]. At week 32, time of glucose values in range (70-180 mg/dl) measured by CGM was 88.9% with CagriSema, 76.2% with semaglutide and 71.7% with cagrinlitide [10]. Another secondary endpoint was weight changes at 32 weeks. In that respect, CagriSema was statistically superior to both semaglutide and cagrilintide. Thus, mean changes in body weight from baseline was -15.6% with CagriSema, -5.1% with semaglutide, and –8.1% with cagrilintide (table 1) [10]. Interestingly, 54% of patients lost ≥15% of weight in the CagriSema group compared with only 7% in the cagrilintide group and none in the semaglutide group [10]. Inspection of the trajectory of weight changes with time revealed that weight loss continued to progress in the CagriSema group up to the end of treatment at 32 weeks, whereas in the semaglutide and cagrinlitide groups, weight reduction seemed to approach a plateau [10].

	Cagrilintide [9]	**CagriSema [10]**
Design	Phase 2, double-blind, randomized, placebo and active controlled (liraglutide), multinational (10 countries)	Phase 2, double-blind, randomized, multicenter in the USA
Duration of follow-up	26 weeks	32 weeks
Subject number and groups	706 subjects without diabetes, 7 groups	92 patients with type 2 diabetes, 3 groups
Subject characteristics	Mean age 52, 62% women, 77% Whites, 13% Asians	Mean age 58, 36% women, 78% Whites, 16% Blacks
Baseline weight, BMI	107.4 kg, 37.8 kg/m^2	105.7 kg, 35.5 kg/m^2
Baseline HbA1c	5.6%	8.4%
Intervention	Cagrinlitide (0.3, 0.6, 1.2, 2.4, 4.5 mg/week), liraglutide 3.0 mg, placebo	Cagrinlitide 2.4 mg, semaglutide 2.4 mg, CagriSema 2.4 + 2.4 mg
Primary outcome	Percentage in weight loss from baseline	Change in HbA1c from baseline
Secondary outcomes	Proportions of subjects losing ≥5% and ≥10% of weight, FPG, CGM parameters, safety	Changes in weight, FPG, CGM parameters, safety
Effect on weight	-6.0 to -10.8% cagrilintide, -9.0% liraglutide, -3.0% placebo	-15.6% CagriSema, -5.1% semaglutide, -8.1% cagrilintide
Effect on HbA1c	0% to -0.1% cagrilintide, -0.3% liraglutide, -0.1% placebo	-2.2% CagriSema, -1.8% semaglutide, -0.9% cagrilintide
Drug discontinuation due to adverse effects	2-6% cagrilintide, 7% liraglutide, 3% placebo	0% CagriSema, 3% semaglutide, 0% Cagrilintide

Abbreviations in table 1. BMI: body mass index, HbA1c: glycated hemoglobin, FPG: fasting plasma glucose, CGM: continuous glucose monitoring

Table 1: Efficacy and safety of cagrilintide monotherapy vs cagrilintide combined with semaglutide (CagriSema) for treatment of obesity and type 2 diabetes

	CagriSema 2.4/2.4 mg/week [10]	Tirzepatide 15 mg/week [12]
HbA1c reduction	2.2% at 32 weeks	2.1% at 72 weeks
Weight loss	15.6% at 32 weeks	12.8% at 72 weeks

Abbreviations: HbA1c; glycated hemoglobin

Table 2: Comparison between CagriSema and tirzepatide for treatment of type 2 diabetes with obesity

Effect of CagriSema on cardiovascular risk factors and leptin

There were no differences between the groups of patients randomized to CagriSema, cagrilintide, and semaglutide in terms of plasma lipid parameters [10]. Meanwhile, reduction in mean systolic blood pressure (SBP) at week 32 was greater with CagriSema (-13 mmHg) compared with cagrilintide (-3 mmHg) and semaglutide (+ 1 mmHg) [10]. Yet, no significant differences were found in diastolic blood pressure [10]. Leptin to soluble leptin receptor ratio decreased at 32 weeks in the CagriSema group versus other groups reflecting increased leptin sensitivity [10]. This ratio did not change in the semaglutide group [10].

Safety of Cagrinlitide and CagriSema

In the obesity trial, the proportions of participants who discontinued study treatment due to adverse events were 2-6%, 7%, and 3% in the cagrilintide, liraglutide and placebo groups, respectively [9]. In the diabetes study, no patients discontinued CagriSema or cagrilintide due to adverse effects, whereas one patient discontinued semaglutide due to adverse effects [10]. The most common adverse effects of CagriSema were GI disorders occurring in 58% of subjects compared with 32% treated with semaglutide and 33% with cagrilintide [10]. Level 1 hypoglycemia (blood glucose 54-69 mg/dl) occurred with more frequency with CagriSema (6%) and cagrilintide (7%) than with semaglutide (0%) [10]. Heart rate increased by 3 beats per minute (bpm) with CagriSema, 7 bpm with semaglutide, and decreased by 1 bpm with cagrilintide [10].

Appraisal of CagriSema for treatment of obesity and type 2 diabetes

1.Advantages of CagriSema

Available data suggest that the HbA1c-lowering efficacy of the combination of cagrilintide and semaglutide was higher than that achieved by each drug alone (table 1) [10]. However, the efficacy of this combination was much less than additive (table 1) [10]. This is possibly due to overlapping anti-hyperglycemic mechanisms shared by both cagrilintide and semaglutide such as delay in gastric emptying and inhibition of postprandial glucagon secretion. On the other hand, in terms of weight loss, available data suggest that the combination of the 2 agonists had a synergistic effect (table 1) [10]. The weight loss caused by CagriSema was substatntial with more than half of patients losing 15% or more of weight at 32 weeks [10]. It should be emphasized that exceeding the cutoff weight loss of 15% is of great clinical importance. Indeed, sustained weight reduction of 15% or more in patients with type 2 diabetes may induce diabetes remission in a large proportion of subjects and improve metabolic status in the remaining patients [11]. While head-to-head comparison is lacking, CagriSema seems more effective in promoting weight reduction than the dual agonist of GLP-1R and gastric inhibitory polypeptide (GIP) receptor, tirzepatide (table 2). The latter is currently considered the most effective incretin-based agent for lowering body weight [12]. The magnitude of weight reduction by CagriSema might be even more pronounced with longer follow-up since no evidence of a plateau effect was demonstrated up to the end of treatment at 32 weeks [10].

2.Limitations of CagriSema

While preliminary results are encouraging, the combination of cagrilintide and semaglutide suffers from multiple limitations. First, GI adverse effects were numerically more common with CagriSema (58%) compared with semaglutide (32%) or cagrilintide (32%) [10]. Second, 7% of patients experienced mild level I hypoglycemia with CagriSema compared to none with semaglutide [10]. It will be interesting to see whether hypoglycemia would become more frequent or more severe if CagriSema is used in patients taking insulin or sulfonylureas. Third, the phase 2 diabetes trial was small including only 30-31 patients in each group [10]. This led to some imbalance in patients' baseline characteristics that may affect the results. For instance, mean duration of diabetes was much shorter in the CagriSema group (6.4 years) compared with semaglutide (9.2 years) and cagrilintide (10.7 years) [10]. The latter imbalance might amplify the glycemic efficacy of CagriSema knowing that new stages of diabetes respond generally better to therapy than later stages. Fourth, the duration of the trial, 32 weeks, was insufficiently long to demonstrate the durability of glycemic and weight effects of CagriSema [10]. Fifth, the patient population did not include various minorities that could respond differently to intervention [10].

Conclusions and current needs

The combination of the amylin analog cagrilintide and the GLP-1R analog semaglutide, called CagriSema, represents a promising novel strategy for treatment of type 2 diabetes and obesity. Preliminary data suggests that this combination is highly effective in promoting weight loss in obese patients with type 2 diabetes in addition to being effective in lowering HbA1c levels [10]. Meanwhile, CagriSema was associated with increased rates of GI adverse effects and mild hypoglycemia. Currently, a series of phase 3 clinical trials, under the name of REDEFINE Program, are underway [13]. These trials should evaluate efficacy and safety of CagriSema in a larger population of subjects affected by obesity with and without diabetes from different ethnic groups and using various background diabetes therapy. In addition, adequately powered long-term studies should be conducted to evaluate the effects of CagriSema on cardiovascular events and mortality.

Conflict of interest

The author has no conflicts of interests to declare.

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