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Injections for weight loss: what's new in GLP-1 RAs for obesity treatment – review

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ABSTRACT

Among the myriad challenges confronting contemporary medicine, the obesity epidemic stands out as one of the most critical, warranting special attention due to its association with numerous severe comorbidities and its significant consumption of both human lives and financial resource. This review presents recent clinical trials addressing the issue of the effects of Glucagon-Like Peptide 1 Receptor Agonists (GLP-1 RAs) in the management of overweight and obesity in non-diabetic patients and identifies areas requiring further investigation.

GLP-1 RAs, initially used in the treatment of type II diabetes, represent some of the most promising pharmacotherapeutic agents for obesity. Their mechanism of action involves lowering glucose levels by stimulating insulin secretion, inhibiting glucagon secretion, and delaying gastric emptying. They also affect the centres of hunger and satiety, contributing to a reduction in food intake, including food cravings. In clinical studies, GLP-1 RAs have demonstrated effectiveness in reducing body weight in both diabetic and non-diabetic patients with fairly good tolerance. The discussion is grounded in three clinical studies that examine the use of liraglutide and semaglutide, and the development of a novel GLP-1 RA, ecnoglutide.

The use of semaglutide and liraglutide is associated with significant weight reduction and a decrease in cardiovascular risk in non-diabetic patients, while ecnoglutide represents a promising new GLP-1 RA that requires further investigation.

Keywords: obesity, weight loss, liraglutide, GLP-1

INTRODUCTION

According to the World Health Organization (WHO), in 1990, overweight affected 25% of adults, while by 2022, this figure had risen to 43%, with 16% of adults suffering from obesity, making it not only a huge problem for health care, but also an economic burden [1-2].

Losing 5-15% of body weight can significantly reduce the risk of obesity-related health problems [3]. Unfortunately, obesity is associated with a high risk of recurrence after initially achieving the desired body weight. Patients affected by obesity face substantial challenges in both losing and maintaining weight, as well as weight-related diseases. Therefore, the introduction of long-term effective treatment methods is crucial for public health [4-5].

A promising group of substances in the pharmacological management of obesity and overweight are Glucagon-Like Peptide 1 Receptor Agonists (GLP-1 RAs), initially developed for treating type 2 diabetes [5-6]. The aim of this review is to present recent research on the use GLP-1 RAs in the treatment of overweight and obesity in adults without diabetes, with a focus on the long-term use of these drugs.

1. STATE OF KNOWLEDGE

1.1. Etiopathogenesis of obesity and weight-related diseases

Obesity is a chronic disease characterized by the presence of excessive amounts of fat tissue in the body, leading to numerous complications [6-7]. Weight gain results from an excess of energy intake over energy expenditure, influenced by numerous factors including environmental influences, genetics, chronic diseases, and medications. However, the recent increase in the incidence of obesity and the projected continuation of this trend are primarily attributed to environmental factors, such as an unhealthy, high-calorie diet and low levels of physical activity [8-9].

Obesity affects multiple systems and organs, and its etiopathogenesis is highly complex. Excess visceral fat plays a critical role in this context. In obese individuals, visceral fat is prone to chronic inflammation, which disrupts adipocyte homeostasis and contributes to the development of metabolic and cardiovascular complications, including disturbances in glucose metabolism, primarily type II diabetes, hypertension, atherosclerosis and its complications, fertility disorders, musculoskeletal system issues, respiratory system problems, certain cancers, and more [10-11].

1.2. Obesity management

The primary approach to treating overweight and obesity involves dietary modifications, behavioural strategies, and increased physical activity [3,12]. For individuals who do not attain reduction in body weight through these methods, and meet certain criteria, supplementary pharmacological or surgical interventions are implemented as an addition to therapy based on a lifestyle-based regimen [3,13].

Pharmacotherapy is advised for patients with a BMI (body mass index) ≥ 30 kg/m² for whom non-pharmacological interventions have been ineffective, as well as for patients with a BMI ≥ 27 kg/m² who present with at least one obesity-related comorbidity and have not achieved the targeted outcomes through non-pharmacological means.

According to polish guidelines, this treatment should be administered for a minimum duration of 6 months, with an optimal duration of at least 12 months [3,13]. Treatment is considered effective if the weight loss is no less than 5% [14].

1.3. GLP-1 RAs in obesity treatment

GLP-1 (Glucagon-Like Peptide 1) is a metabolic hormone released by the intestinal L-cells in response to carbohydrates and lipids in the ileum. Its actions include stimulating insulin secretion in a glucose-dependent manner, inhibiting glucagon secretion, and delaying gastric emptying. It also exerts effects on hunger and satiety centres, thereby reducing hunger and food intake while enhancing feelings of fullness [15-16]. Analogous effects are achieved through the use of GLP-1 RAs, which possess a considerably longer half-life compared to natural GLP-1, thus making them viable for pharmacotherapeutic applications [17]. These drugs were initially introduced as antidiabetic agents but currently, two GLP-1 RAs are approved for the treatment of obesity by EMA (European Medicines Agency) and FDA (Food and Drug Administration): liraglutide, used subcutaneously daily and semaglutide, used subcutaneously weekly or orally daily [3, 18].

Clinical trials have demonstrated that the use of both medications is associated with significant weight loss in adults with overweight or obesity [19-21]. The greatest weight loss is observed with the administration of semaglutide at a dose of 2.4 mg once weekly and liraglutide at doses exceeding 1.8 mg daily. Among these, semaglutide produces the most significant weight reduction, with a more pronounced effect in individuals without diabetes compared to those with the condition [19]. GLP-1 RAs are characterized by relatively good tolerability, although adverse effects are common, particularly with prolonged use and at higher doses. The most frequent side effects are gastrointestinal in nature, especially nausea, and they range in severity from mild to moderate [19, 21]. There are also reports suggesting the potential beneficial effects of this class of drugs on cardiovascular and metabolic risk, not only through weight reduction and carbohydrate metabolism regulation but also through blood pressure reduction, improvement of lipid parameters, liver metabolism, myocardial remodelling post-infarction, and vascular function. However, identifying the underlying mechanisms of action, as well as determining their efficacy and applicability in this regard still requires extensive research [22].

Despite these promising outcomes, GLP-1 RAs have certain limitations. There exists a subset of patients who do not respond to treatment with these agents, as well as a group of patients who experience mild yet bothersome gastrointestinal side effects [23-24]. The high production costs of GLP-1 RAs, the requirement for subcutaneous injections, and the insufficient amount of research on their long-term use—including both their prolonged efficacy and potential adverse effects—also present challenges. Therefore, ongoing research into the currently used medications in this class, as well as the development of new ones, is warranted. One such novel agent is ecnoglutide [25].

RECENT CLINICAL TRAILS

The subsequent studies were selected from publications spanning 2022-2024, identified through a search conducted on PubMed between May 6th and 10th, 2024, using the keywords GLP-1 analogs AND weight loss.

Effect of the glucagon-like peptide-1 receptor agonist liraglutide, compared to caloric restriction, on appetite, dietary intake, body fat distribution and cardiometabolic biomarkers: A randomized trial in adults with obesity and prediabetes

The study was designed to test the hypothesis that the use of liraglutide alone would lead to weight loss and a greater improvement in the fat-to-lean tissue ratio in adults with obesity and prediabetes compared to a reduced-calorie diet. Sitagliptin, a DPP-4 inhibitor (Dipeptidyl peptidase-4 inhibitor), was employed as a comparator with a neutral effect on weight to assess the individual effectiveness of these interventions.

Eighty-eight obese adults (BMI $\geq$ 30 kg/m^2) with prediabetes were randomly assigned to three treatment arms (2:1:1): daily administration of 1.8 mg liraglutide, 100 mg sitagliptin, or a dietary intervention targeting a caloric deficit of 390 kcal below their Resting Energy Expenditure (REE), determined by indirect calorimetry. Notably, 44% of participants in the reduced-calorie diet group achieved a weight loss of at least 5% from baseline, compared to 22% in the liraglutide group and 5% in the sitagliptin group. The diet group exhibited significant improvements in weight and body composition, with a mean reduction in body weight of 4.4 kg versus 2.5 kg in the liraglutide group, a change in the fat-to-lean tissue ratio of -6.5% versus -2.2%, and a visceral fat loss of 9.5% versus 4.8%. Importantly, these changes were not accompanied by a reduction in REE. Participants in the sitagliptin and calorie-restricted diet groups reported heightened feelings of hunger and reduced satiety, whereas those in the liraglutide group reported hunger levels similar to baseline and increased satiety. Moreover, individuals in the diet group exhibited a spontaneous decrease in carbohydrate intake and an improvement in insulin resistance, as indicated by a decrease in the HOMA-IR index.

Liraglutide monotherapy exhibited inferior efficacy compared to a calorie-restricted diet [26].

Two-year effects of semaglutide in adults with overweight or obesity: the STEP 5 trial

The STEP 5 clinical trial investigated the long-term outcomes of weekly subcutaneous administration of 2.4 mg semaglutide compared to placebo in overweight or obese adults without diabetes. The trial had two co-primary endpoints: the change in body weight from baseline at week 104 and the proportion of participants achieving at least a 5% weight loss at week 104.

Initially, the analysis focused on 304 participants selected from non-diabetic adults with obesity (BMI $\geq$ 30 kg/m^2) or overweight (BMI $\geq$ 27 kg/m^2) with at least one weight-related comorbidity. These participants were randomly assigned in a 1:1 ratio to either the semaglutide group or the placebo group, with both groups receiving concurrent behavioural interventions.

Semaglutide led to a significant reduction in body weight at week 104, with 77.1% achieving $\geq$5% weight loss, compared to 34,4% in placebo group. The semaglutide group exhibited a mean reduction in body weight of -15.2%, whereas the placebo group had a reduction of only -

2.6%. Additionally, semaglutide demonstrated improvements in secondary endpoints such as BMI, blood pressure, and metabolic markers.
The majority of adverse events were gastrointestinal in nature, mostly mild to moderate in severity and occurred in a greater proportion of individuals in the semaglutide group compared to the placebo group (82.2% vs. 53.9%).
Despite these adverse events, semaglutide showed superior efficacy and tolerability compared to placebo, indicating its potential as a treatment option for overweight or obese individuals without diabetes [27].

Discovery of ecnoglutide - A novel, long-acting, cAMP-biased glucagon-like peptide-1 (GLP-1) analog
This study aimed to evaluate the safety, tolerability, pharmacodynamics, and pharmacokinetics of ecnoglutide, a novel GLP-1 RAs. It was engineered to prioritize cAMP production over other signals, aiming to enhance long-term glycaemic control and overall efficacy compared to semaglutide. The goal is to create a drug that would be highly effective, better tolerated, more user-friendly and cost-effective than existing market options.
In rodent models, ecnoglutide at a dose of 0.05 mg/kg demonstrated greater reductions in body weight and glycemia, as well as increased insulin secretion compared to semaglutide. A crossover study revealed that rats transitioning from ecnoglutide to semaglutide experienced weight gain, whereas those initially treated with semaglutide followed by ecnoglutide continued to lose weight.
In the phase 1 trial, 64 healthy volunteers were divided: 36 into the Single Ascending Dose (SAD) group, receiving one subcutaneous dose of ecnoglutide or placebo (0.03 to 1.0 mg adjusted by body weight), and 28 into the Multiple Ascending Dose (MAD) group, receiving weekly subcutaneous doses of ecnoglutide (0.2, 0.4, or 0.6 mg over 6 weeks, with gradual escalation over 2 weeks).
Adverse effects primarily included decreased appetite, nausea, and headache, predominantly mild to moderate in severity, with no serious treatment-related adverse events reported. Ecnoglutide's pharmacokinetic profiles in both animal models and humans resembled those of semaglutide, showing a half-life (t1/2) of 124 to 138 hours compared to 165 hours for semaglutide, with greater stability.
The favourable tolerability and pharmacological characteristics of ecnoglutide support its further investigation as a potential therapeutic agent for obesity and type 2 diabetes [25].

SUMMARY

In the cited clinical studies, the use of the investigated GLP-1 RAs, liraglutide and semaglutide, demonstrated beneficial effects in terms of weight reduction and improvement in cardiovascular and metabolic parameters in patients with overweight or obesity, without type II diabetes, while maintaining good tolerance to the treatment [26-27].

Liraglutide at a dose of 1.8 mg per day has demonstrated efficacy in the treatment of obesity and the reduction of cardiometabolic risk. It contributed to weight loss, a reduction in visceral fat, and an improvement in body composition. It is noteworthy that dietary intervention proved more effective than liraglutide monotherapy over the 14-week study period, although the use of liraglutide was associated with a reduced sensation of hunger.

Additionally, it was observed that the reduction in body weight and fat mass in these groups did not correlate with a decrease in resting energy expenditure, which is typically seen in individuals losing weight and is likely a factor in weight regains following weight loss [26].

Semaglutide at a dose of 2.4 mg weekly, combined with behavioural intervention, demonstrated clinically significant efficacy in the treatment of the studied cohort of adults with overweight or obesity without diabetes. This efficacy was observed in terms of weight loss, maintenance of achieved weight loss, as well as improvements in cardiovascular and metabolic parameters over a 104-week period. Additionally, the average weight loss in the studied group was –15.2%, which surpasses the outcomes achieved with liraglutide over a comparable treatment duration [27-29].

In animal models, ecnoglutide has demonstrated efficacy in enhancing insulin secretion and reducing glycemia, as well as superior effectiveness in reducing body weight compared to semaglutide. Moreover, in a Phase I study, in the tested group of healthy volunteers, it exhibited favourable pharmacokinetics with relatively good tolerability. Unlike semaglutide, ecnoglutide is composed solely of natural amino acids, and its production requires fewer steps, making it simpler to manufacture. Additionally, it is more stable than semaglutide, suggesting its potential use in oral form. Therefore, further research on ecnoglutide appears warranted. [25].

GLP-1 RAs represent a promising treatment option for patients with overweight and obesity, particularly in addressing diseases and disorders associated with excessive fat mass. However, it is important to remember that they serve as an adjunct to dietary, behavioural, and physical activity interventions. Implementing and maintaining a healthy lifestyle remains the primary treatment for individuals with obesity. The use of GLP-1 RAs can potentially facilitate the adoption of such a lifestyle and contribute to achieving more substantial and long-term treatment outcomes.

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