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Retatrutide - revolutionary recently developed GLP agonist - literature review

Retatrutyd - rewolucyjny niedawno wynaleziony agonista receptorów GLP - przegląd literatury

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Abstract:

Obesity - defined by excessive amount of fat tissue - is becoming more and more serious health problem among our population and affecting a growing number of people [1]. It is crucial in treatment to encourage and adjust patients to increased physical activity and decreased food consumption. However, it is much easier said than done, resulting in lowered motivation and many failed attempts at patients which makes it more difficult to engage in weight loss process. Holistic approach from medical team is crucial. More drugs are becoming approved in treatment of obesity - which is a big step for patients having a high body mass index (BMI) for whom diet and exercise might not be enough in order to lose weight. One of these drugs is retatrutide which appears to be a game-changer amongst other medications. It is revolutionary since it is a „triple G” agonist - it affects glucagon-like peptide (GLP) receptors, glucose-dependent insulotropic polypeptide (GIP) receptors and glucagon (GCG) receptors. It is a first substance of already available weight loss drugs that affects all three mentioned receptors - eg. semaglutide is a GLP receptor agonist and recently developed tirzepatide is a GLP and GIP receptors agonist. It could lead to revolutionizing weight loss treatments industry, making it even more successful and efficient. The aim of our study is to describe this new drug, its ' mechanism of action and discuss possible benefits versus adverse effects.

Keywords: retatrutide; weight loss; obesity; GLP agonist

Introduction

The percentage of population being currently affected by obesity is increasing [2]. The reports present worrying predictions indicating that within the next 12 years more than half of the global population, will be either obese or overweight. Obesity is taking part in development of plenty of health issues such as cardiovascular diseases, chronic pain, neoplasms, mood disorders and very commonly diabetes mellitus type 2 (DM2). There are few treatment options such as diet restriction, lifestyle adjustment, pharmacotherapy and surgery. Dietary modifications and physical exercises shall be first steps in order to attempt weight loss. Alteration of lifestyle is crucial to overcome obesity, nevertheless it is often not enough or is too difficult to implement among certain group of patients. Some of the factors impacting such decision among patients are dysphoria related to long time required to see the first effects of diet, stigma surrounding obesity, mobility difficulties, poor effects of calories reduction, discountenance, depression. Due to these reasons more and more patients decide to lean on pharmacotherapy instead or opt to combine drugs with diet and increased physical activity. Recently developed medication facilitating weight loss such including retatrutide belong to a group of anti-diabetic drugs and are gaining their attention. In this study we will focus on their activity, effectiveness, risks, adverse effects and availability.

Retatrutide, is a peptide which is not only a GLP-1 agonist, but also shows agonist activity at the glucose-dependent insulintropic polypeptide (GIP) and glucagon (GCG) receptors. It might be extremely valuable and revolutionary since two of the most popular recently introduced weight-loss medications are semaglutide (known as Ozempic) which is a GLP-1 agonist and tirzepatide which is a GLP-1 and GIP agonist, whereas retatrutide affects more receptors than two mentioned above. Retatrutide affects GIP receptors more than GCG and GLP-1 receptors when compared to native hormones. Activating GLP-1 receptors which are present in e.g. pancreas, heart, brain and blood vessels causes lowering glucose concentration in blood (both fasting and after meals) due to regulation of pancreatic secretion of glucacone and insulin. This drug causes weightloss and fat loss due to decreasing calories intake and suppressing appetite - the mechanism of action results in delayed gastric emptying due to affecting glucagon-like peptide-1 and glucagon receptors, which is one of main directions while trying to find effective weight-loss method. Delayed emptying of stomach results in higher satisfaction after consuming less, it extends the period between meals, allowing lower calories intake during the day and limiting the size of portions. Its half-life is circa 6 days which allows

weekly administration through subcutaneous injections [3]. In comparison to tirzepatide it is quite a difference since Mounjaro (tirzepatide) must be injected daily.

Current available research shows promising results, claiming that the weightless effects might be even better than already well-known Ozempic (semaglutide) or recently developed Mounjaro (tirzepatide) (3). Semaglutide administered once weekly at the dose of 50 mg resulted in 15-17% mean weight loss. Tirzepatide led to mean weight loss of 22,5%. Whereas retatrutide dosed between 1 to 12 mg resulted in 24,2 % - not to mention that 36-48% of patients ended with a weight loss above 25% compared to placebo. Increased percentage of lost weight occurred at patients with BMI above 35 kg/m² and in females [4]. These outcomes are very promising and optimistic.

Methodology

An electronic search was completed in PubMed database. Recommendations were extracted from the identified articles and collated as themes. However, the available literature is very limited due to the fact that the reviewed medication is still in clinical trials and is not available to patients yet.

Discussion

It appears weight loss and decreased food intake effects caused by retatrutide might be significantly greater comparing to well known drugs such as semaglutide or long-acting GCG RA, even when combined together. However delayed gastric emptying occurs after at least 10 days of retatrutide treatment, therefore asking patients for patience at the beginning of therapy should be helpful [5].

Retatrutide demonstrates remarkable correlation between dose and response. Phase 2 of vast clinical trial, involved 338 adults with body mass index (BMI) 30 or higher or with BMI 27-30 and at least one weight-related condition. They were assigned to receive subcutaneous retratitide (1mg, 4mg, 8mg,12mg or placebo) once a week for 48 weeks. Study revealed that all patients treated with 8mg and 12mg retratitide reached 5% weight reduction or more by the time of 48 weeks. In addition at least 75% of previously mentioned patients reached 15% weight loss, which can be compared to 60% for 4mg dose and 2% for placebo. However the most

phenomenal was mean weight reduction of 24,2% after 48 weeks. Meanwhile patients were still loosing weight after the treatment was stopped [6].

Another study included 281 participants with type 2 diabetes, elevated glyated haemoglobin - HbA_{1c} (7,0-10,5%) and BMI (25-50 kg/m²) treated previously with healthy diet, exercise and stable dose of metformin for at least 3 months before screening. During study patients maintained healthy diet with exercise and received once a week injections of retratutide (0,5mg, 4mg, 8mg, 12mg), 1,5mg dulaglutide or placebo. Comparable to precending study, reduction in body weight of patients with highest doses of retratutide were remarkable. However there was also significant decrease in HbA_{1c} after 24 weeks – from 0,45% for 0,5mg to 2,02% for 12mg of retratutide, versus 0,01% for placebo and 1,41% for dulaglutide [7].

In a different research [5] on mice retratutide in a dose of 10 nmmol per kg was administered and resulted in reducing body weight - and the weight loss was greater compared to semaglutide and when compared to efficacy of simultaneous administration of of semaglutide and glucagon receptor agonist. These results are also very promising.

Despite the fact that discussed triple-hormone-receptor agonist gives the impression of being exceptionally efficacious, it's adverse effects are still investigated. The most frequent appears to be gastrointestinal disorders, such as nausea, diarrhea, vomiting and constipation, which were commensurate to drug's dose. Additionally hypoglycemia events were not reported. Moreover increased heart rate occurred with its peak at 24 weeks, however it lowered just after. Last but not least the drug's half-life is assumed to be approximately 6 days, which confirms rightness of once-weekly dosing [8]. Nevertheless further research might be required.

Summary

Finally, taking in consideration inconceivable effort and hard work, which must be put in losing weight by seriously obese patients, it appears, that retratutide might be inestimable tool in their life-changing journey through health. As triple-hormone-receptor agonist, it decreases HbA_{1c} level and delays gastric emptying, which affects food intake and promotes weight loss. During treatment patients are experiencing reduction in hunger, which might be used to build healthy habits such as balanced diet and everyday movement. Although the drug is currently in the testing phase it seems to be the answer for future obesity epidemic.

Disclosures

Author's contribution:

Conceptualization Methodology: PB, AF, Software: not applicable; Check: PB, AF, BN, AM, Formal analysis: KP, IL, AF, PB, Investigation: PB, AF, Resources: not applicable; Data curation: Writing - rough preparation: PB, AF, BN, AM, IL, KP, Writing - review and editing: IL, KP, Visualization: BN, AM, Supervision: PB, AF Project administration: PB

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