Review Article

Retatrutide: A triple incretin receptor agonist showing promise in obesity treatment

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Abstract

The increasing prevalence of obesity poses a significant challenge for healthcare providers worldwide. However, the recent advancements in the development of drugs for obesity treatment offer hope for effectively addressing this global health concern. The success of semaglutide and tirzepatide, GLP-1 receptor agonists, in targeting the neuroendocrine mechanisms responsible for obesity represents a significant milestone. The introduction of retatrutide, a novel drug for obesity treatment, is also a promising development for the field.

The ongoing phase 2a clinical trials provide an opportunity to evaluate the safety and efficacy of this new therapeutic option. Aim of this systematic review is to present comprehensive information on the anti-obesity action of this GIP-1 receptor agonist at hand. Detailed research was conducted via the PubMed database using the keywords: "retatrutide" and "obesity or weight loss". No further filters were applied.

Clinical trials have shown substantial weight loss with the use of Retatrutide, in patients with obesity. Further research is necessary to ascertain the safety of this GLP-1 receptor agonist in question and to conduct comparative analyses with other similar agonists. These clinical trials will provide valuable insights into the efficacy and performance of the drug, which will be useful in determining its potential for use in medical treatment for obesity.

KeyWords: retatrutide, obesity, weight loss, GLP-1, GLP-1 Receptor Agonists

Introduction

Retatrutide (LY3437943) is a peptide agonist that binds to GIP, GLP-1, and GCG receptors and is currently being investigated in phase 2 clinical trials. GLP-1 receptor agonists have been found to effectively stimulate insulin production and inhibit the release of glucagon, which plays a crucial role in regulating blood glucose levels. Moreover, these agonists exert a central effect on appetite and food intake, suggesting their potential as a treatment option for obesity.(1) Remarkably, retatrutide has demonstrated promising outcomes in terms of weight reduction during clinical trials.(2)

Materials and methods

Extensive research was conducted using the PubMed database's published bibliography, using precise keywords such as "retatrutide" and "obesity or weight loss". To ensure accuracy, data was extracted using a standard data elicitation form and following PRISMA-ScR guidelines. After an initial search, 13 records were identified, but no additional ones were found through reference review as they were similar to the initial ones. From the PubMed database, 13 full-text articles were assessed for eligibility, and 4 were excluded due to non-relevant abstracts. Upon thorough evaluation, all 9 references have been deemed eligible and relevant for this study, meeting the required criteria for suitability.

Results

Based on the research results, it has been observed that retatrutide has a significant effect on reducing weight and shows great potential in treating obesity in the future. After 48 weeks of treatment with the GLP-1 receptor agonist, the average weight loss percentage in the group receiving a 12-mg dose of retatrutide was approximately 24%. The forthcoming clinical trials will provide important information about the safety and effectiveness of our product in a larger and more diverse population. It is crucial to gather the required data to confidently assess the

comprehensive range of its positive effects.

Discussion

Retatrutide (LY3437943) is an agonist of the glucose-dependent insulinotropic polypeptide, glucagon-like peptide 1, and glucagon receptors. Its mechanism of action involves the stimulation of these receptors, which initiates a series of physiological responses aimed at regulating appetite and metabolism. This, in turn, leads to weight loss and offers promising potential for effectively treating obesity.(1) Results from the phase 1b clinical trial indicate that retatrutide is considered safe, and its pharmacokinetics support a convenient once-weekly dosing regimen, with a maximum dose of 12 mg.(3) It is noteworthy that the study found the impact of increasing dosages of retatrutide, a GLP-1 receptor agonist, on weight loss among individuals with obesity to be dose-dependent. However, it is important to consider that the study's active comparator was dulaglutide, another GLP-1 receptor agonist that is not approved for obesity treatment and was administered at a significantly lower dose of 1.5mg compared to the highest approved dose of 4.5mg. These findings indicate the need for further research to evaluate the efficacy of retatrutide in treating obesity, considering the limitations of the current study.(4) The phase 2 clinical trial included 338 adult participants, with 51.8% men and women comprising the cohort. To be eligible for the study, participants needed to have a body-mass index (BMI) of 30 or higher, or a BMI of 27 to less than 30 along with at least one weight-related condition. The study involved randomized assignment of participants in a 2:1:1:1:1:2:2 ratio to receive subcutaneous retatrutide (1 mg, 4 mg [initial dose, 2 mg], 4 mg [initial dose, 4 mg], 8 mg [initial dose, 2 mg], 8 mg [initial dose, 4 mg], or 12 mg [initial dose, 2 mg]) or placebo once weekly for 48 weeks. The main aim of the study was to determine the percentage change in body weight over a span of 24 weeks. Secondary objectives included assessing the percentage change in body weight after 48 weeks and measuring the reduction in weight of 5%, 10%, or 15%, or more from the initial weight.(5,6,7) After 48 weeks of treatment, the group of participants who received retatrutide showcased a considerable reduction in weight in contrast to the group treated with placebo. The degree of weight loss varied according to the dosage, with the participants in the 1 mg group showing an average percentage change of -8.7%. The combined 4-mg group exhibited an average percentage change of -17.1%, while the combined 8-mg group showed an average percentage change of -22.8%. Notably, the 12-mg group exhibited the greatest average percentage change of -24.2%. In contrast, the placebo group only displayed a modest average percentage change of -2.1%. Furthermore, at the end of the 48-week treatment period, it was observed that a notable 92% of participants who received a dosage of 4 mg of retatrutide experienced a weight reduction of 5% or more. A substantial 75% and 60% of cases also demonstrated a weight reduction of 10% or more and 15% or more, respectively. Similarly, for those administered with 8 mg, the percentages of participants achieving a weight reduction of 5% or more, 10% or more, and 15% or more were 100%, 91%, and 75%, respectively. The highest dosage of 12 mg demonstrated even more promising results, with 100%, 93%, and 83% of participants achieving the respective weight reduction thresholds. In stark contrast, the placebo group only exhibited meager percentages of 27%, 9%, and 2% in terms of weight reduction of 5% or more, 10% or more, and 15% or more, respectively. The data indicates that retatrutide is a promising treatment for weight loss, with higher dosages yielding more significant and consistent results.(5,6,7) During the treatment period, adverse events were observed in a significant proportion of participants in the placebo group and the retatrutide groups, with the highest incidence being recorded in the 8-mg and 12-mg groups. The participants in the retatrutide groups experienced gastrointestinal adverse events, such as nausea, diarrhea, vomiting, and constipation, more frequently than those in the placebo group. These events occurred primarily during the dose escalation period, were mainly mild to moderate in severity, were more frequent in higher-dose groups, and were partially mitigated

by the use of a lower starting dose (2 mg vs. 4 mg). Moreover, gastrointestinal adverse events were the most commonly reported adverse events leading to treatment discontinuation.(5,8) As a side effect, retatrutide has also been found to increase heart rate by up to 6.7 beats per minute.(9)

Conclusions

The use of retatrutide as an intervention for obesity has shown promising results. The group that received retatrutide had a significant weight reduction compared to the group that received the placebo. This suggests that retatrutide could be an effective approach to managing weight loss in obese individuals in the near future. The available evidence suggests that retatrutide may be more effective than other GLP-1 receptor agonists. However, it is important to note that such comparisons may not be meaningful, and further research is necessary to establish the safety of retatrutide in larger and more extended trials. It is important to weigh the benefits and risks of any medication before initiating treatment. Healthcare providers must be aware of potential complications. Further research is needed to fully understand the mechanisms behind these effects and to determine whether certain patient populations may be at higher risk for experiencing these side effects.

References

1. Seetharaman R, Pandit S. Breaking the mold: revolutionary new obesity drugs set to transform treatment landscape? J Basic Clin Physiol Pharmacol. 2023 Aug 16;34(6):689-690. doi: 10.1515/jbcpp-2023-0172. PMID: 37581246.

2. Harris E. Triple-Hormone Combination Retatrutide Induces 24% Body Weight Loss. JAMA. 2023 Jul 25;330(4):306. doi: 10.1001/jama.2023.12055. PMID: 37405802.

3. Doggrell SA. Is retatrutide (LY3437943), a GLP-1, GIP, and glucagon receptor agonist a step forward in the treatment of diabetes and obesity? Expert Opin Investig Drugs. 2023 May;32(5):355-359. doi: 10.1080/13543784.2023.2206560. Epub 2023 Apr 24. PMID: 37086147.

4. Ray A. Retatrutide: a triple incretin receptor agonist for obesity management. Expert Opin Investig Drugs. 2023 Jul-Dec;32(11):1003-1008. doi: 10.1080/13543784.2023.2276754. Epub 2023 Nov 24. PMID: 37902090.

5. Jastreboff AM, Kaplan LM, Frías JP, Wu Q, Du Y, Gurbuz S, Coskun T, Haupt A, Milicevic Z, Hartman ML; Retatrutide Phase 2 Obesity Trial Investigators. Triple-Hormone-Receptor Agonist Retatrutide for Obesity - A Phase 2 Trial. N Engl J Med. 2023 Aug 10;389(6):514-526. doi: 10.1056/NEJMoa2301972. Epub 2023 Jun 26. PMID: 37366315.

6. Elfeki MA, Alkhouri N. Triple-Hormone-Receptor Agonist Retatrutide for Obesity. N Engl J Med. 2023 Oct 26;389(17):1629. doi: 10.1056/NEJMc2310645. PMID: 37888926.

7. Jastreboff AM, Kaplan LM, Hartman ML. Triple-Hormone-Receptor Agonist Retatrutide for Obesity. Reply. N Engl J Med. 2023 Oct 26;389(17):1629-1630. doi: 10.1056/NEJMc2310645. PMID: 37888927.

8. Bisson A, Fauchier G, Fauchier L. Triple-Hormone-Receptor Agonist Retatrutide for Obesity. N Engl J Med. 2023 Oct 26;389(17):1628. doi: 10.1056/NEJMc2310645. PMID: 37888925.

9. Doggrell SA. Retatrutide showing promise in obesity (and type 2 diabetes). Expert Opin Investig Drugs. 2023 Jul-Dec;32(11):997-1001. doi: 10.1080/13543784.2023.2283020. Epub 2023 Nov 24. PMID: 37947489.