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The Era for Dual and Triple Receptor Agonists Treating Type 2 Diabetes (T2D)

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Abstract

Recent trends for the treatment of type 2 diabetes (T2D) show dual or triple receptor agonists for incretins peptides. They are glucagon-like peptide-1 (GLP-1), glucose-dependent insulinotropic polypeptide (GIP) and glucagon (GCG). Triple receptor agonist includes LY3437943, in which clinical efficacy for 12 weeks was glucose -3.1 mmol/L, HbA1c -1.6% and weight -8.96 kg. Dual agonist includes tirzepatide (GIP/GLP-1) that shows remarkable efficacy for lowering blood glucose for T2D patients. Tirzepatide (10 mg/day) showed 20% of weight reduction at 72 weeks and was also effective for heart failure with preserved ejection fraction (HFpEF), non-alcoholic steatohepatitis (NASH) and major adverse cardiovascular events (MACE).

Keywords: ***Triple receptor agonist; Dual receptor agonist; Incretin peptide; Glucagon-like peptide-1 (GLP-1); Glucose-dependent insulinotropic polypeptide (GIP); Glucagon (GCG); Tirzepatide***

Glucose control and homeostasis would be in focus for several incretin hormones [1]. They include dual or triple incretin peptides, which are from glucagon-like peptide-1 (GLP-1), glucose-dependent insulinotropic polypeptide (GIP) and glucagon (GCG) [2]. Concerning the novel treatment for Type 2 Diabetes (T2D), latest report was presented in Nov, 2022 [3]. The agent is the triple receptor agonist, which shows remarkable effects for T2D. The investigation was conducted for the safety of LY3437943, which has GCG, GIP and GLP-1 receptor agonist. The protocol included 72 cases of T2D in US, and pharmacodynamics and pharmacokinetics were studied by multicenter, double-blind, phase 1b, randomized, placebo-controlled, multiple dose escalation. Participants for this study were provided three types of treatments for 12 weeks at random, which were LY3437943 (escalation cohorts for 5 doses), placebo, or dulaglutide 1.5 mg subcutaneously.

As a result, the applicants were given placebo (n=15), dulaglutide 1.5mg (n=5), LY3437943 0.5 mg, 1.5 mg, 3 mg (n=9,9,11), and 3/6 mg, 3/6/9/12 mg (n=11,12). Adverse events were observed in 63% for LY3437943, 60% for dulaglutide 1.5 mg, and 54% for placebo group. Frequent symptoms were gastrointestinal (GI) tract disturbances. Pharmacokinetics was dose proportional manner associated with about 6 days of half-time period. Clinical effects were compared for mean glucose level at 12 weeks in three groups [3]. The decreased glucose degree was 2.8, 3.1 and 2.9 mmol/L for 3 mg, 3/6 mg and 3/6/9/12 mg, respectively. Similarly, HbA1c improvement was 1.4%, 1.6% and 1.2%, respectively. Weight reduction was dose-dependent associated with the maximum level to 8.96kg for the 3/6/9/12 mg group. Consequently, LY3437943 presented acceptable safety profile with clinical efficacy, suggesting suitability and efficacy for once-weekly administration. These results indicate robust improvement in glucose and weight and suggest future support for phase 2 study.

As to the problem of obesity, muti-receptor agonists may offer new approaches for this problem. For the basic research of LY3437943 in vitro, balanced GLP-1R and GCGR activity was found, associated with more GIPR activity. When providing LY3437943 to obese mice, weight and glycemic control were improved. Weight reduction was strengthened by increased GCGR agonism for energy expenditure, in addition to decreased calory intake by GKP-1R and GIPR agonism. During phase 1 study for single increasing dose, it presented tolerability and safety as other incretins. It can be provided once-weekly dosing, and weight reduction was observed until day 43 by single dose [4].

For rodent models, combination of unimolecular triple incretins showed the reduction in weight and improvement of glucose variability, which includes GLP-1, GIP and GCG [5]. A synthetic peptide agonist of these three receptors was developed as SAR441255, that was originally based on the sequence of exendin-4. It has high ability of activation of three target receptors in balance. For healthy human, it improved glucose variability during meal tolerance test (MMT). As a result, integrating GIP into GCG and GLP-1 receptor agonism can give higher efficacy of glycemic control and weight reduction, while weakening the diabetogenic risk by glucagon function [5].

LY3437943 and SAR441255 are triple receptor agonist, while some agents are dual agonists. Recently, tirzepatide has been introduced, which is a dual GIP/GLP-1 receptor agonist. It showed remarkable efficacy for lowering blood glucose for T2D patients [6]. Consequently, clinical effect of tirzepatide has been from concurrent improvements for diabetic pathophysiology, which are beta-cell secretion function, insulin resistance and glucagon secretion. This efficacy may explain the remarkable improvement of diabetic variability observed in phase 3 studies [6]. Tirzepatide has been under investigation for clinical use of several pathophysiological situation. They include the control of weight reduction, obesity, heart failure with preserved ejection fraction (HFpEF), non-alcoholic steatohepatitis (NASH), major adverse cardiovascular events (MACE), and others. For assessment of effect and safety, the phase 3 SURPASS 1-5 clinical studies were designed for tirzepatide injection subcutaneously (5, 10, 15 mg/day), monotherapy vs combined treatment [7].

For tirzepatide, phase 3 double-blind, randomized, controlled trials were conducted for 2539 adults with high BMI [8]. Applicants were divided into 1:1:1:1 ratio for receiving once-weekly, subcutaneous injection (5,10,15 mg) or placebo group for 72 weeks. At baseline, mean data were weight 104.8kg, and BMI 38.0. At 72 weeks, weight reduction was 15.0% for 5 mg, 19.5% for 10 mg and 20.0% for 15 mg, and 3.1% for placebo ($p<0.001$ each for placebo). By the treatment of tizepatide,

all prespecified cardiometabolic measures were improved. Regarding adverse events, most common problems were from gastrointestinal system. They were mild to moderate degree, which occurred mainly during dose escalation.

Glucagon (GCG) has been known for its clinical effect of increasing blood glucose. It can also decrease body weight by elevating metabolic rate and reducing food intake. Furthermore, glucagon promotes lipid oxidation/ lipolysis and show positive chronotropic/inotropic efficacy in the heart [9]. Challenging research for developing effective agents for obesity has been observed for decade. They include mono-agonists of the GLP-1R, and also dual GIPR/GLP-1R co-agonists, which can show substantial weight reduction for experimental animals and for humans. For adult humans, GCG receptor agonism can increase energy consumption to negative energy balance. From preclinical investigation, glucagon-GCGR system may influence liver and adipose tissue to boost body thermogenic capacity of the body and to protect weight gain [10].

The research for dual GLP-1 and GCG receptor agonist has been found. It is phase 2a study (NCT03550378) of cotadutide for T2D and chronic kidney disease (CKD) [11]. Participants showed significant reduction for glucose AUC against mixed-MTT as (-26.7% vs +3.7%), and for target glucose range by CGM as (+14.8% vs -21.2%) and for weight reduction as (-3.4 kg vs -0.13 kg) versus placebo group. When providing to CKD cases, urinary albumin-to-creatinine ratio was decreased by 51% on day 32 compared with placebo group. Thus, these results suggest potential efficacy of cotadutide on renal function [11]. GLP-1/GCG receptor co-agonist JNJ-64565111 was investigated for effect and safety. For 195 participants, weight reduction was -4.6%, -5.9%, -7.2% for 5.0 mg, 7.4 mg, 10.0 mg, respectively [12]. It showed significant weight reduction in a dose-dependent manner, without the reduced HbA1c.

In summary, latest trends of dual and triple incretin agonists were described in this article. Further development for these agents would be expected in the future.

REFERENCES

1. Zhao F, Zhou Q, Cong Z, et al. Structural insights into multiplexed pharmacological actions of tirzepatide and peptide 20 at the GIP, GLP-1 or glucagon receptors. Nat Commun. 2022;13(1):1057.
2. Conlon JM, O'Harte FPM, Flatt PR. Dual-agonist incretin peptides from fish with potential for obesity-related Type 2 diabetes therapy - A review. Peptides. 2022;147:170706.
3. Urva S, Coskun T, LohwMT, et al. LY3437943, a novel triple GIP, GLP-1, and glucagon receptor agonist in people with type 2 diabetes: a phase 1b, multicentre, double-blind, placebo-controlled, randomised, multiple-ascending dose trial. Lancet. 2022;400(10366):1869-81.
4. Coskun T, Urva S, Roell WC, et al. LY3437943, a novel triple glucagon, GIP, and GLP-1 receptor agonist for glycemic control and weight loss: From discovery to clinical proof of concept. Cell Metab. 2022;34(9):1234-47.e9.
5. Bossart M, Wagner M, Elvert R, et al. Effects on weight loss and glycemic control with SAR441255, a potent unimolecular peptide GLP-1/GIP/GCG receptor triagonist. Cell Metab. 2022;34(1):59-74.e10.
6. Heise T, Mari A, DeVries JH, et al. Effects of subcutaneous tirzepatide versus placebo or semaglutide on pancreatic islet function and insulin sensitivity in adults with type 2 diabetes: a multicentre, randomised, double-blind, parallel-arm, phase 1 clinical trial. Lancet Diabetes Endocrinol. 2022;10(6):418-29.

7. De Block C, Bailey C, Wysham C, et al. Tirzepatide for the treatment of adults with type 2 diabetes: an endocrine perspective. Diabetes Obes Metab. 2023;25(1):3-17.
8. Jastreboff AM, Aronne LJ, Ahmad NN, et al. Tirzepatide Once Weekly for the Treatment of Obesity. N Engl J Med. 2022;387(3):205-16.
9. Zeigerer A, Sekar R, Kleinert M, et al. Glucagon's Metabolic Action in Health and Disease. Compr Physiol. 2021;11(2):1759-83.
10. Conceição-Furber E, Coskun T, Sloop KW, et al. Is Glucagon Receptor Activation the Thermogenic Solution for Treating Obesity? Front Endocrinol (Lausanne). 2022;13:868037.
11. Parker VER, Hoang T, Schlichthaar H, et al. Efficacy and safety of cotadutide, a dual glucagon-like peptide-1 and glucagon receptor agonist, in a randomized phase 2a study of patients with type 2 diabetes and chronic kidney disease. Diabetes Obes Metab. 2022;24(7):1360-9.
12. Di Prospero NA, Yee J, Frustaci ME, et al. Efficacy and safety of glucagon-like peptide-1/glucagon receptor co-agonist JNJ-64565111 in individuals with type 2 diabetes mellitus and obesity: A randomized dose-ranging study. Clin Obes. 2021;11(2):e12433.